The American Journal of Cardiology®

COK-H01245-61-P024187

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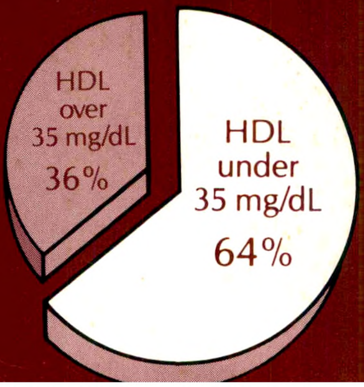
240 TOTAL

<35 HDL

mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]


HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]

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Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 3 times a month in January, April and December, 2 times in July and August, 4 times in February, March, May, June and November, and 5 times in September and October, by Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Robert T. Brawn, Senior Vice President/General Manager; Jerry D. Neth, Senior Vice President/Publishing Operations; J.J. Walsh, Senior Vice President/Finance; Thomas J. Dellamaria, Senior Vice President/Production and Manufacturing. Executive, Editorial and Advertising Offices: 249 West 17th Street, New York, NY 10011. Printed in Easton, PA.
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Predictors of Long-Term Cardiac Survival in Patients with Multivessel Coronary Artery Disease Undergoing Percutaneous Transluminal Coronary Angioplasty

Michel Vandormael, Ubeydullah Deligonul, Sue Taussig, and Morton J. Kern

The predictors of 5-year survival in patients with multivessel coronary artery disease undergoing percutaneous transluminal coronary angioplasty were analyzed in a series of 637 patients. Left ventricular function was the most important determinant in cardiac survival, independent of the clinical success of the procedure. Advanced age and diabetes mellitus were associated with additional risk in the overall group, but not in the successfully treated group. In patients with multivessel CAD, 5-year survival after PTCA is excellent in the absence of these adverse prognostic factors.

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Outcomes of Direct Coronary Angioplasty for Acute Myocardial Infarction in Candidates and Non-Candidates for Thrombolytic Therapy

Bruce R. Brodie, Richard A. Weintraub, Thomas D. Stuckey, E. Joseph LeBauer, Jeffrey D. Katz, Thomas A. Kelly, and Charles J. Hansen

Direct coronary angioplasty was performed in 383 patients with acute myocardial infarction who were classified as candidates or non-candidates for thrombolytic therapy. The reperfusion rates and the incidence of nonfatal reinfarction and recurrent ischemia were similar in the 2 groups. Thrombolytic candidates had a significantly lower mortality rate and a lower incidence of bleeding. Left ventricular ejection fraction improved in both groups. Our results suggest that direct angioplasty is a viable alternative method of reperfusion in candidates for thrombolytic therapy, and may also benefit patients in subgroups of nonthrombolytic candidates, such as patients in cardiogenic shock and those presenting after 6 hours of chest pain with evidence of ongoing ischemia.

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Severity of Single-Vessel Coronary Arterial Stenosis and Duration of Angina as Determinants of Recruitable Collateral Vessels During Balloon Angioplasty Occlusion

Jan J. Piek, Jacques J. Koolen, Gerard Hoedemaker, George K. David, Cees A. Visser, and Arend J. Dunning

Standardized contrast injection of the contralateral artery was performed in 58 patients, without previous myocardial infarction, undergoing percutaneous transluminal coronary angioplasty for 1-vessel disease. This study indicates that a patient with 1-vessel disease and ≥70% diameter stenosis but with a short duration of angina (<3 months) is unlikely to have developed collateral vessels and is at high risk when sudden occlusion of the diseased vessel occurs.

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Characteristics of Black Patients Admitted to Coronary Care Units in Metropolitan Seattle: Results from the Myocardial Infarction Triage and Intervention Registry (MITI)

Charles Maynard, Paul E. Litwin, Jenny S. Martin, Manuel Cerqueira, Peter J. Kudenchuk, Mary T. Ho, J. Ward Kennedy, Leonard A. Cobb, Sharon M. Schaeffer, Alfred P. Hallstrom, and W. Douglas Weaver

Since 1988, 641 black and 11,892 white patients with chest pain of presumed cardiac origin were admitted to coronary care units in 19 hospitals in metropolitan Seattle. Despite differences in age, referral patterns, and the use of coronary angioplasty and bypass surgery, black and white patients with myocardial infarction had similar outcomes.

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Late Results of 200 Repeat Coronary Artery Bypass Operations

Hans A. Verheul, Adrian C. Moulijn, Sjoerd Hondema, Michiel Schouwink, and Arend J. Dunning

Two-hundred consecutive coronary artery bypass reoperations were performed to determine clinical outcome and long-term results. Reoperation is effective but carries an increased, immediate, operative risk. Reoperation often represents a late stage in coronary artery disease with limited prospects, but for patients with severe angina it will offer enough benefits to warrant a second operation.

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Myron H. Luria, Jacob Erel, Dan Sapoznikov, and Mervyn S. Gotsman

Lipid, rheologic, clinical and arteriographic profiles of 380 consecutive patients were divided into quartiles according to the ratio of total cholesterol to high-density lipoprotein cholesterol. Clustering of high- and low-level risk factors was seen in the highest and lowest cholesterol ratio quartiles, respectively, suggesting that this ratio may serve as a marker for a cluster of potentially modifiable coronary artery disease risk factors.

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Prevalence of Unsuspected Mitral Regurgitation and Left Ventricular Diastolic Dysfunction in Patients with Coronary Artery Disease and Acute Pulmonary Edema Associated with Normal or Depressed Left Ventricular Systolic Function

Gregg W. Stone, Brian Griffin, Prediman K. Shah, Daniel S. Berman, Robert J. Siegel, Stephen L. Cook, and Gerald Maurer, with the technical assistance of David E. Brown and Kenneth J. Resser

In 40 patients with coronary artery disease presenting with acute pulmonary edema, isolated left ventricular diastolic dysfunction was found in <30% of patients, regardless of the status of LV systolic function. Moderate to severe mitral regurgitation, frequently silent, was present in nearly two-thirds of all patients. Unrecognized MR may be an important contributing factor to acute pulmonary edema in patients with coronary artery disease.

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Ventricular Tachycardia and Accelerated Ventricular Rhythm Presenting in the First Month of Life

George F. Van Hare and Paul Stanger

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Exercise Thallium-201 Imaging in Complete Left Bundle Branch Block and the Prevalence of Septal Perfusion Defects

Besher Jazmati, Ara Sadaniantz, Susan P. Emaus, and Gary V. Heller

The records of 93 consecutive patients with complete left bundle branch block who underwent symptom-limited treadmill exercise testing with thallium-201 imaging were reviewed to determine the prevalence of septal defects in a generalized referral population. The study demonstrates a low prevalence of septal defects (14%) in a large population of unselected patients presenting for thallium-201 testing. Exercise thallium-201 imaging remains a useful procedure for evaluating patients with complete left BBB.

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Characterization of Spontaneous Termination of Sustained Ventricular Tachycardia Associated with Coronary Artery Disease

David J. Callans and Francis E. Marchlinski

To determine the degree of cycle length variability before spontaneous termination of ventricular tachycardia, we measured cycle lengths for the periods of 31 to 21 beats and 11 to 1 beats before termination in 55 episodes from 29 patients. Changes in QRS morphology were rarely documented before termination and thus did not account for the increase in cycle length variability, whereas antiarrhythmic agents did enhance the tendency toward greater cycle length variability at this time.

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Duration of the QT Interval and Total and Cardiovascular Mortality in Healthy Persons (The Framingham Heart Study Experience)

Robert J. Goldberg, James Bengtson, Zuoyao Chen, Keaven M. Anderson, Emanuela Locati, and Daniel Levy

Baseline electrocardiograms of 5,125 original subjects from the Framingham Heart Study were measured to examine the relation of the QT interval corrected for heart rate to long-term risk of total mortality, sudden cardiac death and death due to coronary artery disease. Results failed to demonstrate an association between baseline QTc and overall mortality, and deaths due to sudden cardiac events or coronary artery disease in a large cohort of essentially healthy persons.

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Comparison of Lisinopril Versus Atenolol for Mild to Moderate Essential Hypertension

D. Gareth Beevers, Roger A. Blackwood, Simon Garnham, Michael Watson, Abdul A. Mehrzad, Karim Admani, Jennifer E. Angell-James, Morgan Feely, Shubha Kumar, Murtaza H. Husaini, David Mannering, Carol Connett, and Christine Long

We compared lisinopril (10 to 40 mg) and atenolol (50 to 100 mg) in 144 patients with essential hypertension in a randomized, double-blind study. Although both lisinopril and atenolol produced comparable reductions in sitting and standing diastolic BP after 8 weeks of treatment, lisinopril produced a significantly greater reduction ($p < 0.05$) in sitting systolic BP.

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Hemodynamic Effects of Renin Inhibition by Enalkiren in Chronic Congestive Heart Failure

Gerald W. Neuberg, Marrick L. Kukin, Joshua Penn, Norma Medina, Madeline Yushak, and Milton Packer

To investigate the hemodynamic effects of renin inhibition in patients with chronic congestive heart failure, we administered enalkiren (1.0 mg/kg) intravenously to 9 patients. The drug completely suppressed plasma renin activity and produced increases in cardiac index and decreases in left ventricular filling pressure, mean right atrial pressure, heart rate and systemic vascular resistance. Renin inhibition is hemodynamically beneficial and may be a novel approach to interfering with the renin-angiotensin system in patients with chronic CHF.

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Effects of Bucindolol on Neurohormonal Activation in Congestive Heart Failure

Eric J. Eichhorn, A. Iain McGhie, John B. Bedotto, James R. Corbett, Craig R. Malloy, Barbara A. Hatfield, David Deitchman, John E. Willard, and Paul A. Grayburn

Fifteen men had assessments of hemodynamics and supine peripheral renin and norepinephrine levels before and after 3 months of therapy with bucindolol. Beta-adrenergic blockade with bucindolol may reduce neurohumoral activation in congestive heart failure, but the changes in plasma renin activity and norepinephrine may not predict hemodynamic improvement.

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Fuminobu Ishikura, Seiki Nagata, Masashi Akaike, Jun Tamai, and Kunio Miyatake

The relations between changes in atrial natriuretic peptide, transmitral pressure gradient, heart rate and blood pressure were studied during exercise in 16 patients with mitral stenosis before and after percutaneous transvenous mitral commissurotomy. Results suggest that the most important factor influencing the secretion of ANP during exercise is the change in transmitral pressure gradient.

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Robert R. Wolfe, James P. Loehr, Michael S. Schaffer, and James W. Wiggins, Jr.

Ketamine, the most frequently used anesthetic agent for cardiac catheterization procedures in children with congenital heart disease, may alter pulmonary vascular resistance or reactivity data during the procedure. Because the primary indication for cardiac catheterization in this age of noninvasive diagnostic technology is to obtain pulmonary vascular resistance or reactivity data in order to establish the feasibility of surgery, it is recommended that ketamine not be used in children undergoing cardiac catheterization.

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Douglas H. Israel, Warren Sherman, John A. Ambrose, Samin Sharma, Noam Harpaz, and Michael Robbins

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Some Good Cardiologic Books Published in 1990

William C. Roberts

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Aloka Color Doppler Scanning Technolog
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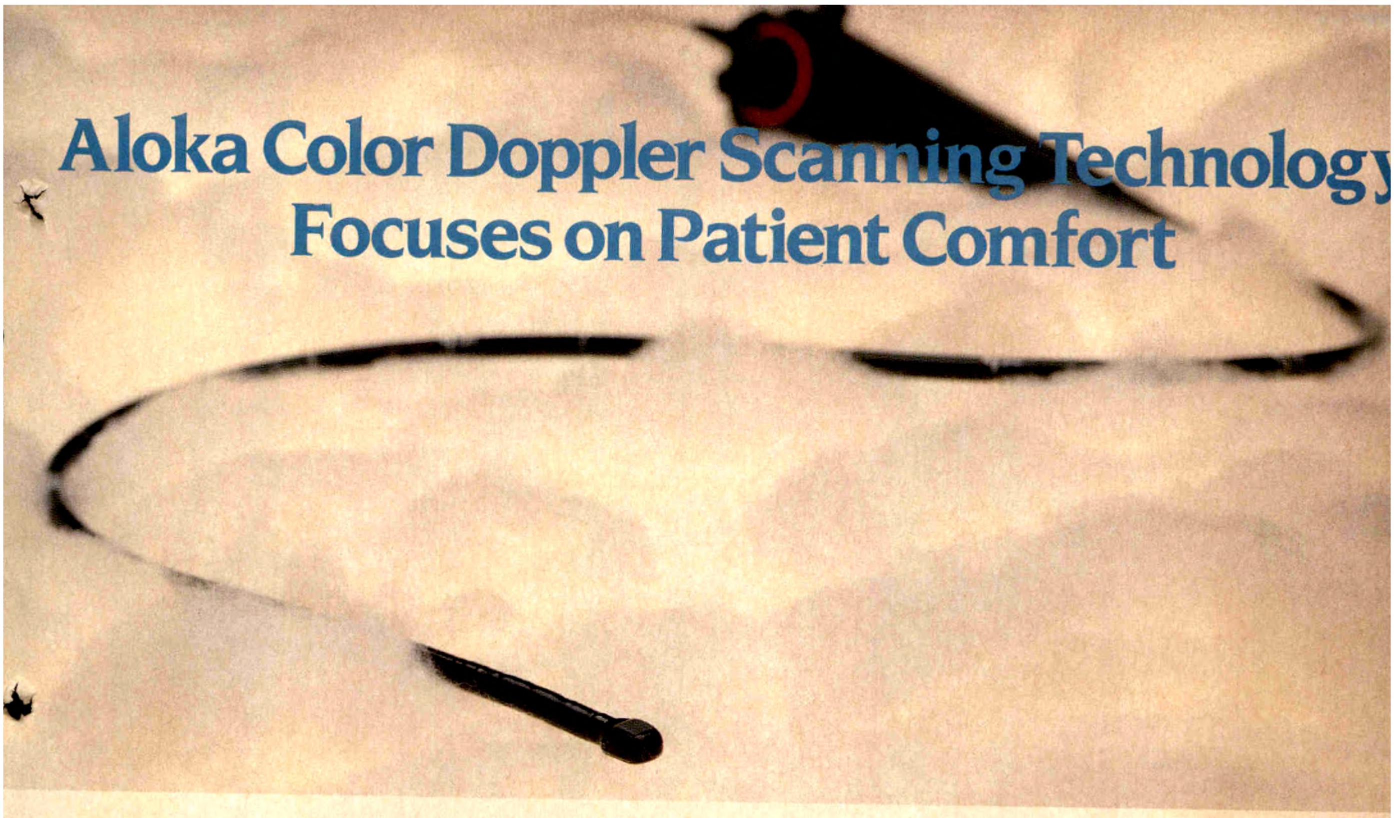

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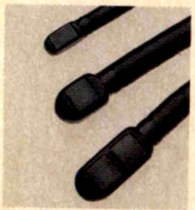

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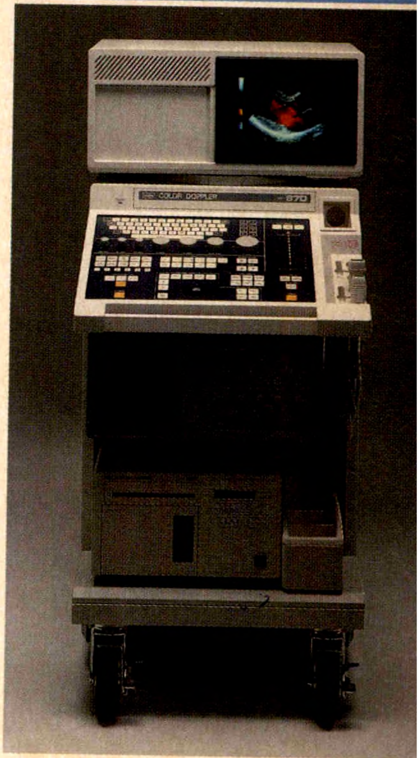

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The American Journal of Cardiology®

JANUARY 1, 1991, VOL. 67, NO. 1

CORONARY ARTERY DISEASE

1

Predictors of Long-Term Cardiac Survival in Patients with Multivessel Coronary Artery Disease Undergoing Percutaneous Transluminal Coronary Angioplasty

Michel Vandormael, Ubeydullah Deligonul, Sue Taussig, and Morton J. Kern

The predictors of 5-year cardiac survival in patients with multivessel coronary artery disease (CAD) undergoing percutaneous transluminal coronary angioplasty (PTCA) were analyzed in a series of 637 consecutive patients. Angiographically, 460 patients had 2-vessel CAD and 177 patients had 3-vessel CAD. The left ventricular contraction score was ≥ 12 in 55 patients. PTCA was clinically successful in 526 (83%) of the 637 patients. Complete revascularization was obtained in 177 of 526 successful patients. Follow-up for ≥ 1 year and up to 6 years after PTCA was obtained in 608 (95%) of the 637 patients. To determine the predictors of 5-year cardiac survival, 28 clinical, angiographic and procedural variables were analyzed by Cox proportional-hazards regression. The estimated 5-year survival after PTCA was 88 ± 2% in successful patients and 77 ± 5% in patients with failed PTCA ($p < 0.001$). When clinical success was forced into the Cox regression, left ventricular contraction score ≥ 12, diabetes mellitus and age ≥ 65 years showed additional adverse effects on survival. When analysis was limited to 503 patients with clinical success and ≥ 1 year complete follow-up, the only independent predictor of cardiac mortality was the left ventricular score ≥ 12. In conclusion, left ventricular function was the most important determinant of cardiac survival in patients with multivessel CAD undergoing PTCA, independent of the clinical success of the procedure.

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Outcomes of Direct Coronary Angioplasty for Acute Myocardial Infarction in Candidates and Non-Candidates for Thrombolytic Therapy

Bruce R. Brodie, Richard A. Weintraub, Thomas D. Stuckey, E. Joseph LeBauer, Jeffrey D. Katz, Thomas A. Kelly, and Charles J. Hansen

Direct coronary angioplasty was performed in 383 patients presenting with acute myocardial infarction (AMI) who were considered either can-

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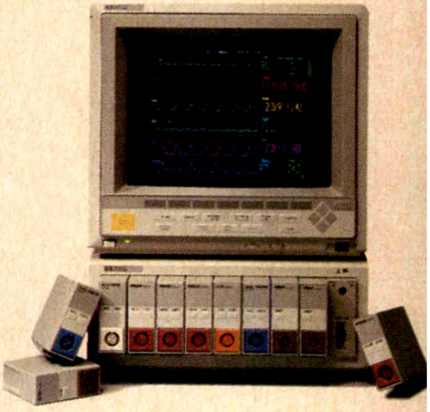

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didates or non-candidates for thrombolytic therapy. Outcomes in thrombolytic and nonthrombolytic candidates were similar in terms of reperfusion rate (92 vs 88%), nonfatal reinfarction (6.0 vs 5.9%) and recurrent ischemia (1.8 vs 0%). Thrombolytic candidates had a significantly lower mortality rate (3.9 vs 24%, p <0.0001) and a lower incidence of bleeding (4.6 vs 10.9%, p <0.05). Improvement in left ventricular ejection fraction at follow-up angiography was 4.4% in thrombolytic and 10.5% in nonthrombolytic candidates (p <0.002) and was greatest in patients with anterior infarctions. These outcomes suggest that direct angioplasty is a viable alternative method of reperfusion in patients who are candidates for thrombolytic therapy. Nonthrombolytic candidates are a very high-risk group of patients for whom direct angioplasty may be beneficial, especially for subgroups of patients in cardiogenic shock and for subgroups of patients presenting after 6 hours of chest pain with evidence of ongoing ischemia.

13

Severity of Single-Vessel Coronary Arterial Stenosis and Duration of Angina as Determinants of Recruitable Collateral Vessels During Balloon Angioplasty Occlusion

Jan J. Piek, Jacques J. Koolen, Gerard Hoedemaker, George K. David, Cees A. Visser, and Arend J. Dunning

Standardized contrast injection of the contralateral coronary artery was performed in 58 patients undergoing percutaneous transluminal coronary angioplasty for 1-vessel disease. The presence of collateral vessels during coronary occlusion was related to clinical, angiographic and electrocardiographic parameters. Collateral vessels during coronary occlusion showed a weak correlation to the percent diameter stenosis before angioplasty (r = 0.28) and to the duration of angina (r = 0.37). Collateral vessels were particularly related to the combination of a lesion severity ≥70% and duration of angina ≥3 months (p <0.001).

18

Characteristics of Black Patients Admitted to Coronary Care Units in Metropolitan Seattle: Results from the Myocardial Infarction Triage and Intervention Registry (MITI)

Charles Maynard, Paul E. Litwin, Jenny S. Martin, Manuel Cerqueira, Peter J. Kudenchuk, Mary T. Ho, J. Ward Kennedy, Leonard A. Cobb, Sharon M. Schaeffer, Alfred P. Hallstrom, and W. Douglas Weaver

Since 1988, 641 black and 11,892 white patients with chest pain of presumed cardiac origin were admitted to coronary care units in 19 hospitals in metropolitan Seattle. In a subset of 2,870 patients with myocardial

Continued on page A25

infarction, blacks (n = 121) were younger, had less prior coronary artery surgery and more prior hypertension, and were more often admitted to central city hospitals. During hospitalization, whites (n = 2,749) had higher rates of coronary angioplasty and coronary artery bypass surgery, although thrombolytic therapy and cardiac catheterization were used equally in the 2 groups. Hospital mortality for black and white patients was similar after multivariate adjustment for key demographic and clinical variables. Despite differences in age, referral patterns, and the use of coronary angioplasty and bypass surgery, black and white patients with myocardial infarction in metropolitan Seattle had similar outcomes.

24

Late Results of 200 Repeat Coronary Artery Bypass Operations

Hans A. Verheul, Adrian C. Moulijn, Sjoerd Hondema, Michiel Schouwink, and Arend J. Dunning

In the present study of 200 consecutive coronary artery bypass reoperations without an additional surgical procedure, an operative mortality of 7.5% and an additional operative cardiac morbidity of 11.5% was found. Cumulative survival after 5 years was 84% and the probability of a cardiac-related event-free period (myocardial infarction, angioplasty, third operation or cardiac death) at 5 years was 64%. Clinical status at the end of follow-up was good in 79.5% of the patients and 35% had no complaints. This result declined over time, and 5 years after the operation almost 50% of the patients had severe angina pectoris again. A reoperation often represents a late stage in coronary artery disease with limited prospects in the long term, but for patients with severe angina it will offer enough benefits to warrant a second operation.

31

Cardiovascular Risk Factor Clustering and Ratio of Total Cholesterol to High-Density Lipoprotein Cholesterol in Angiographically Documented Coronary Artery Disease

Myron H. Luria, Jacob Erel, Dan Sapoznikov, and Mervyn S. Gotsman

We evaluated 380 consecutive patients at the time of coronary angiography with lipid, rheologic, clinical and arteriographic profiles. Patients were then divided by quartile according to the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol (total/HDL cholesterol). Clustering of high- and low-level risk factors was demonstrated in the highest and lowest total/HDL cholesterol quartiles, respectively ($p < 0.001$). The highest quartile may be characterized by an only moderately elevated total cholesterol level but patients in this quartile may have a very low HDL cholesterol level, high triglycerides, a tendency toward high hemoglobin and fibrinogen levels, a history of smoking, previous myocardial infarction and multivessel disease. These results suggest that total/HDL cholesterol serves as a marker for a cluster of potentially modifiable risk factors.

37

Prevalence of Unsuspected Mitral Regurgitation and Left Ventricular Diastolic Dysfunction in Patients with Coronary Artery Disease and Acute Pulmonary Edema Associated with Normal or Depressed Left Ventricular Systolic Function

Gregg W. Stone, Brian Griffin, Prediman K. Shah, Daniel S. Berman, Robert J. Siegel, Stephen L. Cook, and Gerald Maurer, with the technical assistance of David E. Brown and Kenneth J. Resser

This study of 40 patients with coronary artery disease and acute pulmonary edema demonstrated evidence of normal systolic left ventricular (LV) function in 27% of patients. Isolated LV diastolic dysfunction was noted in <30%, regardless of the status of LV systolic function, whereas moderate to severe mitral regurgitation (MR), frequently silent, was present in nearly two-thirds of all patients. Thus, unrecognized MR may be an important contributing factor to acute pulmonary edema in patients with coronary artery disease.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

42

Ventricular Tachycardia and Accelerated Ventricular Rhythm Presenting in the First Month of Life

George F. Van Hare and Paul Stanger

Fourteen infants aged <1 month presented with ventricular tachycardia (VT) or accelerated ventricular rhythm and a structurally normal heart. In 2, VT was associated with long QT syndrome. Twelve had accelerated ventricular rhythm, of whom 2 died before age 2 months of unrelated conditions. Ten are alive at a median age of 4 years. Hemodynamic compromise did not occur with accelerated ventricular rhythm. The ventricular rate was <12% faster than the sinus rate, and the mean QRS duration averaged twice that in sinus rhythm. Treatment was successful in 4 of 5 treated infants and was successfully withdrawn in all. The 10 survivors are free of accelerated ventricular rhythm and off antiarrhythmic medications at follow-up. In view of the excellent long-term outcome and lack of hemodynamic compromise during accelerated ventricular rhythm, it seems reasonable to withhold antiarrhythmic therapy in such infants and await resolution of the rhythm.

46

Exercise Thallium-201 Imaging in Complete Left Bundle Branch Block and the Prevalence of Septal Perfusion Defects

Besher Jazmati, Ara Sadaniantz, Susan P. Emaus, and Gary V. Heller

To evaluate the prevalence of septal defects in patients with complete left bundle branch block (BBB) in a generalized referral population, the records of 93 patients with this condition undergoing exercise thallium-

Continued on page A30

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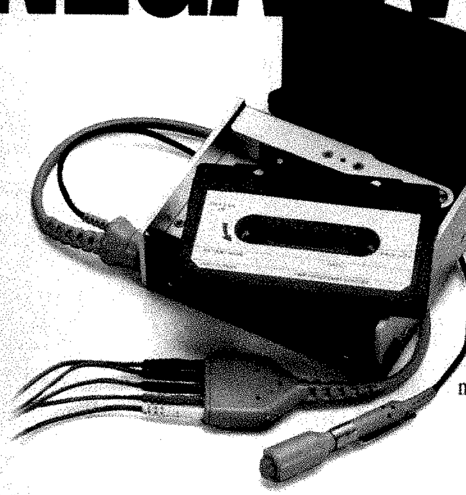

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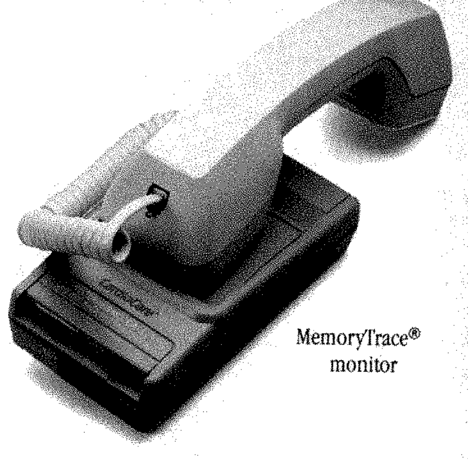

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References: **1.** Klootwijk P, Leenders CM, Roelandt J. Usefulness of transtelephonic documentation of the electrogram during sporadic symptoms suggestive of cardiac arrhythmias. *Int J Cardiol.* 1986;13:155-161. **2.** Data on file, Medtronic CardioCare.

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201 imaging were reviewed. Analysis revealed that 51% of patients had normal and 49% had abnormal images. Of the abnormal studies, only 13 patients had septal defects, whereas 33 (39%) had a much higher percentage of inferior or apical defects, or both. Thus, this study demonstrates a low prevalence (14%) of septal defects in a large population of unselected patients. These data suggest that exercise thallium-201 imaging is useful in evaluating patients with complete left BBB.

50

Characterization of Spontaneous Termination of Sustained Ventricular Tachycardia Associated with Coronary Artery Disease

David J. Callans and Francis E. Marchlinski

To determine the degree of cycle length variability before spontaneous termination of ventricular tachycardia (VT), we measured cycle lengths for the periods of 31 to 21 beats and 11 to 1 beats before termination in 55 episodes from 29 patients. Significantly greater variability occurred 11 to 1 beats before termination than over a period of stable tachycardia (31 to 21 beats); however, marked cycle length variability (>40 ms) was also seen in the absence of termination. Changes in QRS morphology were rarely documented before termination and thus did not account for the increase in cycle length variability. Antiarrhythmic agents enhanced the tendency toward greater cycle length variability at the time of VT termination. These results have important implications for our understanding of antiarrhythmic drug action, for validation of computer models of VT termination and for defining protocols for antitachycardia pacemakers.

55

Duration of the QT Interval and Total and Cardiovascular Mortality in Healthy Persons (The Framingham Heart Study Experience)

Robert J. Goldberg, James Bengtson, Zuoyao Chen, Keaven M. Anderson, Emanuela Locati, and Daniel Levy

The baseline electrocardiograms of 5,125 original subjects from the Framingham Heart Study were measured to examine the relation of QT interval corrected for heart rate (QTc) to long-term risk of total mortality, sudden cardiac death and death due to coronary artery disease. Quintiles of QTc (seconds) were studied in relation to these outcomes. There were no significant differences in the risk of total mortality, sudden cardiac death or death due to coronary artery disease according to QTc. A similar lack of significant association between QTc and these outcomes was observed among all persons studied and in the 2 sexes after using multivariate regression analyses. The results of this study fail to demonstrate an association between baseline QTc and overall mortality, and deaths due to sudden cardiac events or coronary artery disease in a large cohort of essentially healthy persons.

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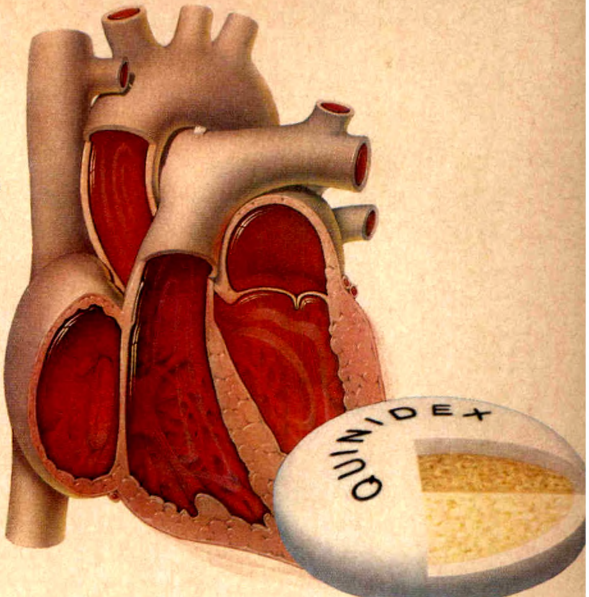

B.I.D.

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	**Effect**
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

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SYSTEMIC HYPERTENSION

59

Comparison of Lisinopril Versus Atenolol for Mild to Moderate Essential Hypertension

D. Gareth Beevers, Roger A. Blackwood, Simon Garnham, Michael Watson, Abdul A. Mehrzad, Karim Admani, Jennifer E. Angell-James, Morgan Feely, Shubha Kumar, Murtaza H. Husaini, David Mannering, Carol Connett, and Christine Long

This randomized, double-blind study compared lisinopril (10 to 40 mg) and atenolol (50 to 100 mg) in 144 patients with essential hypertension. After 8 weeks of treatment, both lisinopril and atenolol produced comparable reductions in sitting and standing diastolic blood pressure (BP). However, lisinopril produced a significantly greater reduction ($p < 0.05$) in sitting systolic BP. Both drugs were well tolerated and no important changes in the hematologic or biochemical variables occurred. The study suggests that lisinopril, like atenolol, may be of value as first-line therapy in essential hypertension.

CONGESTIVE HEART FAILURE

63

Hemodynamic Effects of Renin Inhibition by Enalkiren in Chronic Congestive Heart Failure

Gerald W. Neuberg, Marrick L. Kukin, Joshua Penn, Norma Medina, Madeline Yushak, and Milton Packer

We investigated the hemodynamic effects of renin inhibition in 9 patients with chronic heart failure by using enalkiren, a primate-selective, dipeptide renin inhibitor. Enalkiren (1.0 mg/kg) administered intravenously completely suppressed plasma renin activity (8.4 ± 2.8 ng/ml/hour to values <0.2 ng/ml/hour) and produced increases in cardiac index (1.97 ± 0.25 to 2.31 ± 0.14 liter/min/m^2) and decreases in left ventricular filling pressure (31.0 ± 2.7 to 24.9 ± 2.9 mm Hg), mean right atrial pressure (15.4 ± 1.4 to 13.0 ± 1.9 mm Hg), heart rate (78 ± 5 to 72 ± 6 beats/min) and systemic vascular resistance (2,199 ± 594 to 1,339 ± 230 dynes·s·cm^{-5}) (all $p < 0.01$ to 0.05). Hence, renin inhibition produces hemodynamic benefits in heart failure and may potentially provide a novel approach to interfering with the renin-angiotensin system in patients with this disorder.

Continued on page A35

67

Effects of Bucindolol on Neurohormonal Activation in Congestive Heart Failure

Eric J. Eichhorn, A. Iain McGhie, John B. Bedotto, James R. Corbett, Craig R. Malloy, Barbara A. Hatfield, David Deitchman, John E. Willard, and Paul A. Grayburn

To examine the effects of β-adrenergic blockade on neurohormonal activation in patients with congestive heart failure, 15 male patients had assessments of hemodynamics and supine peripheral renin and norepinephrine levels before and after 3 months of oral β-blocker therapy. At baseline, norepinephrine levels had a weak correlation with left ventricular end-diastolic pressure, stroke volume index and pulmonary vascular resistance. Plasma renin levels decreased with β-blocker therapy, whereas plasma norepinephrine was unchanged. Although plasma norepinephrine did not decrease, heart rate tended to decrease with β-adrenergic blockade, suggesting neurohormonal antagonism at the receptor level. No changes in I-123 metaiodobenzylguanidine uptake occurred after β-blocker therapy, suggesting unchanged norepinephrine uptake with β-blocker therapy. The response of renin or norepinephrine levels to long-term bucindolol therapy did not predict which patients had improved in hemodynamic status. Thus, β-adrenergic blockade with bucindolol may reduce neurohormonal activation in congestive heart failure, but the changes in plasma renin activity and norepinephrine may not predict hemodynamic improvement.

VALVULAR HEART DISEASE

74

Effects of Percutaneous Transvenous Mitral Commissurotomy on Levels of Plasma Atrial Natriuretic Peptide During Exercise

Fuminobu Ishikura, Seiki Nagata, Masashi Akaike, Jun Tamai, and Kunio Miyatake

To clarify the factors that influenced the secretion of human atrial natriuretic peptide (ANP) during exercise, the relations between changes in ANP, transmitral pressure gradient, heart rate and blood pressure were studied during exercise in 16 patients with mitral stenosis before and after percutaneous transvenous mitral commissurotomy (PTMC). Before and after PTMC, ANP levels increased after exercise testing concomitant with the increment in mean transmitral pressure gradient, heart rate and systolic blood pressure. However, increments of ANP, mean transmitral pressure gradient and heart rate after PTMC were lower than those before PTMC. To determine the most important factor influencing the secretion of ANP, the differences between these parameters were calculated at

Continued on page A39

*CAPOTEN (captopril tablets) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

submaximal exercise before and after PTMC. There was a significant relation only between the change in ANP and that in mean transmitral pressure gradient ($r = 0.70$, $p < 0.01$). These results suggest that the most important factor influencing the secretion of ANP during exercise is the change in transmitral pressure gradient.

79

Blood Rheology After Cardiac Valve Replacement with Mechanical Prostheses or Bioprostheses

Renate Koppensteiner, Anton Moritz, Werner Schlick, Gabriele Fenzl, Susanne Roedler, Herbert Ehringer, and Ernst Wollner

Hemorrheologic determinants—fibrinogen, plasma viscosity, red cell aggregation, hematocrit and platelet aggregation—were studied in 92 patients with mechanical bileaflet valves, in 28 patients with bioprostheses and in 29 healthy control subjects. Fibrinogen, plasma viscosity, and red cell and spontaneous platelet aggregation were increased in all patients with substitute heart valves compared with control subjects; among patients, fibrinogen, plasma viscosity and spontaneous platelet aggregation were higher in patients with mechanical valves than in patients with bioprostheses, whereas no difference could be found for red cell aggregation. Rheologic abnormalities may contribute to thrombus formation at the site of the artificial valve by further disturbing blood flow in regions of flow stagnation created in the immediate vicinity of the prosthetic device.

CONGENITAL HEART DISEASE

84

Hemodynamic Effects of Ketamine, Hypoxia and Hyperoxia in Children with Surgically Treated Congenital Heart Disease Residing ≥1,200 Meters Above Sea Level

Robert R. Wolfe, James P. Loehr, Michael S. Schaffer, and James W. Wiggins, Jr.

Ketamine is the anesthetic agent most often used for cardiac catheterization procedures in pediatric patients with congenital heart disease. Since the advent of sophisticated noninvasive diagnostic equipment, one of the few indications for cardiac catheterization is to obtain accurate pressure data. If ketamine alters pulmonary vascular resistance, it would negate the primary reason for the procedure. Pulmonary and systemic vascular resistance ratios and reaction to hypoxia identified 3 groups: normal, intermediate and hyperresponders. Normal responders had a normal resistance ratio (0.11) in room air and had little resistance ratio response to hypoxia (+0.02), hyperoxia (−0.03) or ketamine (+0.01). Intermediate responders had a slightly elevated resistance ratio (0.20) in room air, and a moderate reaction to hypoxia (+0.13), hyperoxia (−0.08) and ketamine (+0.11). Hyperresponders had an elevated resistance ratio (0.42) in room air, and a striking reaction to hypoxia (+0.61), hyperoxia (−0.17) and ketamine (+0.49). Ketamine should not be used in children undergoing procedures to establish operability based on pulmonary vascular resistance or pulmonary vascular reactivity.

BRIEF REPORTS

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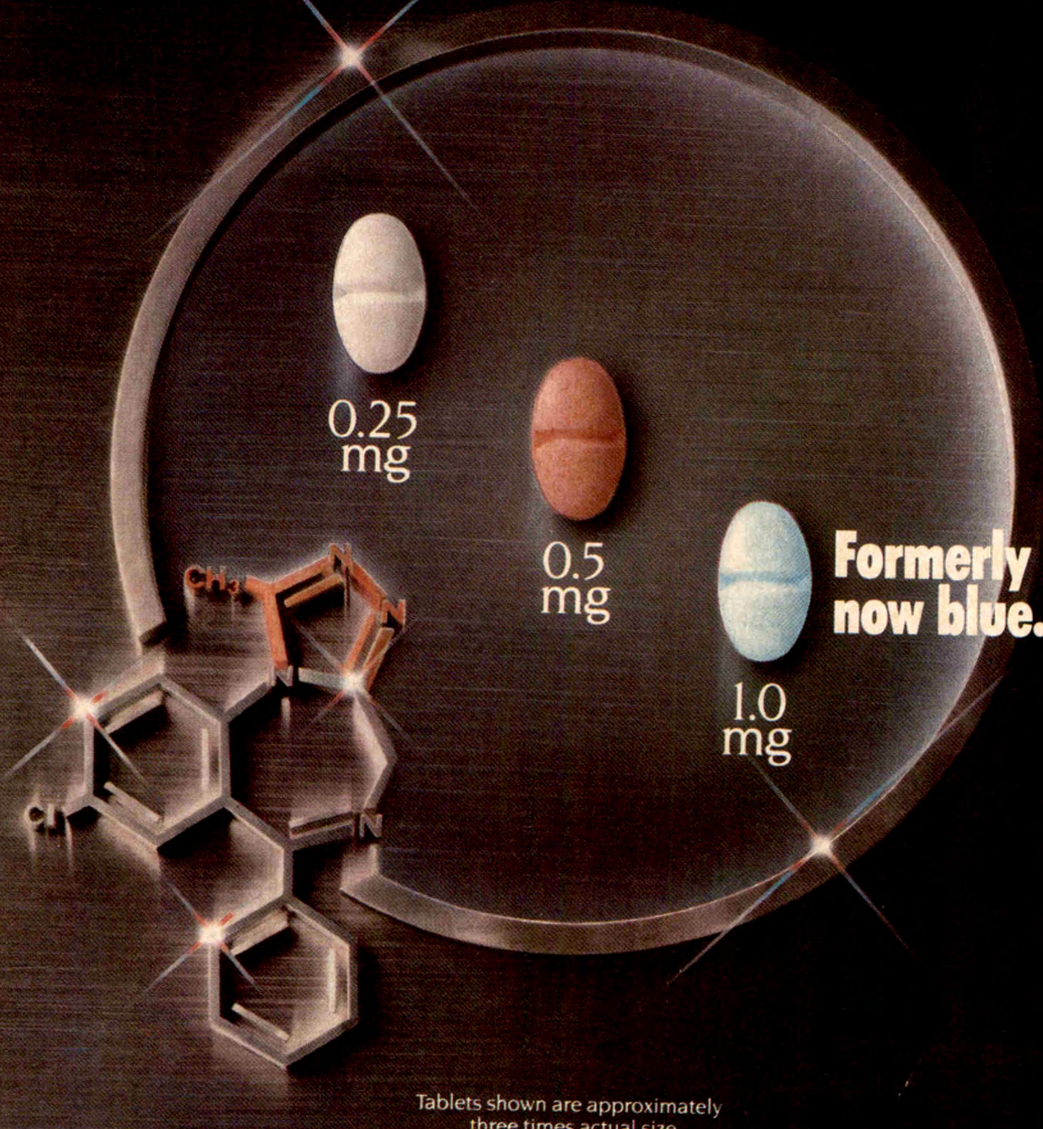

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CASE REPORT

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Dynamic Coronary Ostial Obstruction Due to Papillary Fibroelastoma Leading to Myocardial Ischemia and Infarction

Douglas H. Israel, Warren Sherman, John A. Ambrose, Samin Sharma, Noam Harpaz, and Michael Robbins

FROM THE EDITOR

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Some Good Cardiologic Books Published in 1990

William C. Roberts

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

JANUARY 1, 1991, VOL. 67, NO. 1

Predictors of Long-Term Cardiac Survival in Patients with Multivessel Coronary Artery Disease Undergoing Percutaneous Transluminal Coronary Angioplasty

Michel Vandormael, MD, Ubeydullah Deligonul, MD, Sue Taussig, RN, and Morton J. Kern, MD

The predictors of 5-year cardiac survival in patients with multivessel coronary artery disease (CAD) undergoing percutaneous transluminal coronary angioplasty (PTCA) were analyzed in a series of 637 consecutive patients. The average age was 59 ± 11 years in 472 men and 165 women. Diabetes mellitus, previous myocardial infarction and unstable angina were present in 119 (19%), 261 (41%) and 305 (47%) patients, respectively. Angiographically, 460 patients had 2-vessel and 177 patients had 3-vessel CAD. The left ventricular contraction score was ≥12 in 55 patients. Angiographic success (<50% residual stenosis) was achieved in 85% of the 1,343 narrowings and clinical success was obtained in 526 (83%) of the 637 patients. Complete revascularization was obtained in 177 (34%) of 526 successful patients. Procedure-related complications resulted in death in 9 patients (1.4%), in Q-wave myocardial infarction only in 6 patients (0.9%) and in emergency bypass surgery in 44 patients (6.9%) (of whom 10 had Q-wave myocardial infarction). Follow-up for ≥1 year and up to 6 years after PTCA was obtained in 608 (95%) of the 637 patients. To determine the predictors of 5-year cardiac survival, 28 clinical, angiographic and procedural variables were analyzed by Cox proportional-hazards regression. The estimated 5-year survival after PTCA was 88 ± 2% in successful patients and 77 ± 5% in patients in whom PTCA was unsuccessful (p <0.001). When clinical success was forced into the Cox regression, the left ventricular contraction score of ≥12, diabetes mellitus and age ≥65 years showed additional adverse effects on survival. When analysis was limited to 503 patients with clinical success and ≥1 year complete follow-up, the only independent predictor of cardiac mortality was the left ventricular score of ≥12.

In conclusion, left ventricular function was the most important determinant of cardiac survival in patients with multivessel CAD undergoing PTCA, independent of the clinical success of the procedure. Advanced age and diabetes mellitus were associated with additional risk in the overall group, but not in the successfully treated group. In patients with multivessel CAD, 5-year survival after PTCA is excellent in the absence of these adverse prognostic factors.

(Am J Cardiol 1991;67:1–6)

Although percutaneous transluminal coronary angioplasty (PTCA) is now being widely applied in patients with multivessel coronary artery disease (CAD), many questions regarding indications, patient selection and long-term outcome remain unanswered. Several studies with intermediate-term follow-up (average 15 to 31 months) have shown a mortality rate of 2% and a nonfatal myocardial infarction rate of 2 to 3% during the first 2 years after the procedure.[1-8] In these series, a second revascularization procedure was required in 25 to 30% of patients, most often during the first year. The second revascularization procedure performed was coronary artery bypass surgery in approximately two-thirds of patients and repeat PTCA in others.

There are only limited data on longer (≥4 years) follow-up after PTCA in patients with multivessel CAD. The follow-up results are often presented only in patients with clinically successful procedures, with less emphasis on the impact of unsuccessful or complicated PTCA on the overall long-term outcome. Although several factors have been related to survival with medical or surgical treatment of CAD, the determinants of survival after PTCA in patients with multivessel CAD are not well known.

In this study, we analyzed the predictors for long-term survival in a large series of consecutive patients

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TABLE I Clinical and Angiographic Characteristics

	No.	%
Total	637	
Age	59 ± 11 (29–94)	
Male/female	472/165	74/26
Diabetes mellitus*	119	19
Systemic hypertension*	284	44
Cigarette smoking*	246	39
Previous (>1 week) myocardial infarction	261	41
Unstable angina	305	47
Angina ≥ (Canadian Cardiac Society) class III	403	63
Two-vessel CAD	460	72
All proximal narrowings	137	30
Proximal LAD + proximal LC	18	
Proximal LAD + proximal right	74	
Proximal LC + proximal right	45	
One proximal narrowing	260	57
Total occlusion	123	27
Proximal	104	
Distal	19	
Three-vessel CAD	177	28
All proximal narrowings	21	12
One or more proximal narrowing	152	86
Total occlusion	74	42
Proximal	48	
Distal	26	
LV score ≥12	55	9

* Definition of coronary risk factors is based on patient history; diabetes mellitus = treatment by diet, oral antidiabetic drugs or insulin of elevated blood sugar; systemic hypertension = a previous diagnosis of high blood pressure or treatment by diet or antihypertensive therapy, or both; cigarette smoking = any tobacco smoking habit continued within 1 year of percutaneous transluminal coronary angioplasty.

CAD = coronary artery disease; LAD = left anterior descending artery; LC = left circumflex artery; LV = left ventricular.

with multivessel CAD undergoing PTCA to provide guidelines for better selection and follow-up care of the patients.

METHODS

Patients: Six hundred and thirty-seven consecutive patients with multivessel CAD underwent initial PTCA at our institution between May 1983 and June 1988. The patient selection criteria, cardiac catheterization and coronary angioplasty procedures have been previously described.[8] Briefly, the patients were selected on the basis of suitability of culprit lesion(s) to PTCA. In general, all patients were surgical candidates, although a small number of "salvage" PTCA procedures were performed. The patients with prior coronary bypass surgery and those with acute transmural myocardial infarction within 1 week of PTCA were not included in this study.

Angiographic evaluation: Multivessel coronary disease was defined as diameter stenosis of ≥50% of 2 major coronary arteries as determined by averaging the caliper measurements in 2 views. Patients with narrowings in the diagonal branches were considered as having left anterior descending CAD. Patients with stenosis in the obtuse marginal branches were considered as having circumflex CAD. Thus, when a patient had dilatation of diagonal and left anterior descending coronary narrowings, this patient was considered to have had 1-vessel, multilesion dilatation. The lesion location was classified as proximal (proximal, mid- and distal segments of right coronary artery, left anterior descending artery before first septal branch and left circumflex artery before first obtuse marginal branch) and distal (posterior descending and posterolateral branches of right coronary artery, mid- and distal segments of left anterior descending and diagonal branches, and marginal branches and distal part of the left circumflex artery). The extent of residual coronary disease immediately after the PTCA procedure was evaluated by the number, severity (50 to 69, 70 to 99 and 100%) and location (proximal versus distal) of lesions. The presence of ≥70% proximal left anterior descending artery narrowings was also included in the analysis as a separate variable.

Left ventricular function was assessed on 30° right anterior oblique ventriculograms by using a contraction score according to the Coronary Artery Surgery Study coding system.[9] A left ventricular contraction score of ≥12 was selected to identify patients with significant left ventricular dysfunction. In the Coronary Artery Surgery Study registry, a left ventricular score of ≥12 was a predictor of poor outcome in medically treated patients.[10] Left ventricular ejection fraction was not available in all patients; therefore, it was not included in the analysis.

Evaluation of percutaneous transluminal coronary angioplasty results: Angiographic and clinical success and degree of revascularization were defined as previously described.[5] Briefly, coronary artery narrowings were considered successfully dilated when a 30% reduction in luminal diameter stenosis was obtained and the residual narrowing was <50%. Clinical success was defined as successful dilatation of the critical stenosis or of all attempted lesions without exacerbation of symptoms and without major in-hospital complications, such as myocardial infarction, the need for coronary bypass grafting or death. Complete revascularization was defined as successful dilatation of all major coronary or branch vessels and absence of residual stenosis of >50% in a major coronary vessel. Our strategy was to attempt dilation of all significant narrowings during the same procedure. Dilation of occluded vessels that supplied akinetic left ventricular segments was not routinely attempted.

Follow-up: All patients were eligible for ≥1 year of follow-up. The functional status of the patients and presence or absence of cardiac events (acute myocardial infarction, coronary bypass surgery, repeat PTCA) were prospectively determined by questionnaire, telephone interview or clinic visit at 6 months and 1 year after the PTCA and then at 1-year intervals. The medical records (discharge summary, catheterization or PTCA reports, operative records) were obtained to document the occurrence of nonfatal events. Only 7 patients (6 with a second revascularization and 1 with myocardial infarction) refused to release their medical information. Therefore, the events in these 7 patients were defined according to the patient's descriptions. The deaths that occurred as a result of clearly described noncardiac causes (such as cancer, accidents, and so forth) were classified as noncardiac deaths and the remaining deaths were accepted as cardiac deaths. No

TABLE II Results of Percutaneous Transluminal Coronary Angioplasty

	No.	%
Total	637	
No. of lesions dilated/attempted	1,133/1,343	85
Clinical success	526	83
Complete revascularization	177	34
Incomplete revascularization	349	66
Reason for incomplete revascularization		
Total occlusion	171	49
>70% narrowing	88	25
50–70% narrowing	90	26
Remaining narrowing(s) after PTCA		
Single narrowing	274	79
Multiple narrowings	75	21
Proximal narrowing	196	56
Proximal total occlusion	97	28
Proximal LAD >70%	13	4
Complications		
Procedure-related death*	9	1.4
Emergency coronary bypass surgery		
No myocardial infarction	34	5.3
With myocardial infarction	10	1.6
Q-wave myocardial infarction	6	0.9

* Procedure-related death was defined as death occurring immediately in the catheterization laboratory or later in the hospital as a documented, direct result of a complication of PTCA.

LAD = left anterior descending artery; PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Five-Year Outcome of Percutaneous Transluminal Coronary Angioplasty in Multivessel Disease

Cardiac Events*	Whole Group (n = 637) No.	%	Successfully Treated Group (n = 526) No.	%
With complete follow-up†	608	95	503	96
Noncardiac death	12	1.9	10	1.9
Cardiac death	61	10	40	7.6
Nonfatal myocardial infarction	36	5.9	20	3.9
Emergency coronary bypass surgery	44	7.2	—	—
Elective coronary bypass surgery	114	18.7	58	11
Repeat PTCA	73	12	72	13.7

* Mutually exclusive categories in listed order.

† Fifteen additional patients had incomplete follow-up, no events; 5 additional patients had incomplete follow-up, events not included in this table; 9 patients were lost to follow-up.

PTCA = percutaneous transluminal coronary angioplasty.

verification of cause of death was attempted other than available records and family's description.

Statistical analysis: All statistical analyses were performed using the BMDP program.[11] Survival analysis was performed by the Kaplan-Meier method. The noncardiac deaths were censored at the time of death. The group survival differences were compared using the Mantel-Cox test. Clinical, angiographic and procedural factors included in Tables I and II were analyzed in a Cox regression model for cardiac survival. The angiographic and procedural variables were selected for analysis to indicate the extent and severity of CAD before and after PTCA. Cox regression analysis was performed in the overall patient group (including patients who had successful and unsuccessful PTCA) by forcing the clinical success variable into the regression model and then entering other variables in a stepwise fashion to determine additional independent effects on survival. A second analysis was performed only in clinically successful patients to determine the predictors of out-of-hospital survival. Relative risk ratio for each independent variable was calculated from relative risks for favorable and unfavorable values of each variable.[12]

RESULTS

The clinical and angiographic characteristics of the patients are summarized in Table I. Seventy-two percent of patients had 2-vessel and 28% of patients had 3-vessel CAD.

Immediate percutaneous transluminal coronary angioplasty results: An angiographic success was obtained in 85% of narrowings and clinical success was obtained in 83% of patients (Table II). Complete revascularization was obtained in 177 of 526 patients who had clinical success (34%) (Table II). The major complications of the PTCA procedure are listed in Table II.

Follow-up results: A total of 608 patients (95%) had complete follow-up data with ≥1 year of follow-up updated within 6 months of the study deadline. Twenty additional patients had incomplete follow-up, 5 of whom had various events (coronary bypass surgery in 4 and PTCA in 1) that were not included in the analysis. Nine patients were completely lost to follow-up. The incidences of cardiac events (mutually exclusive) for the whole group and for the group with clinically successful PTCA are listed in Table III. The 30-day mortality rate for the whole group was 3.2% (21 patients). PTCA was performed as a salvage procedure in 4 of these 21 patients. The indication for second revascularization in 130 patients with an initially successful PTCA procedure was restenosis in 67 (51%), progression of CAD in 21 (16%) and combined restenosis and progression in 22 (17%). Incomplete revascularization at the initial PTCA was the indication for second revascularization in only 13 (10%) patients. In 6 patients, angiography was not performed or was unavailable, and 1 patient underwent valve surgery after successful PTCA.

Predictors of cardiac mortality: The cardiac survival estimated by the Kaplan-Meier analysis was 93 ± 1, 92 ± 1, 90 ± 1, 88 ± 1 and 86 ± 2% at 1 through 5 years, respectively, in the overall group. The number of patients at risk for these estimates were 509, 419, 307, 175 and 62 at 1 through 5 years, respectively. Clinical success was associated with more favorable 5-year cardiac survival (88 ± 2%) compared with survival in patients with unsuccessful PTCA (77 ± 5%) ($p < 0.001$) (Figure 1). This difference was mostly related to early mortality in patients with failed PTCA (complicated or noncomplicated but unsuccessful) procedures. The Cox regression analysis was first performed in the overall group of 637 patients to include the possible effects of an unsuccessful procedure and complications, such as myocardial infarction and emergency bypass surgery, on survival. According to this analysis (Table IV), left ventricular contraction score of ≥12, diabetes mellitus and age were independent predictors of cardiac mortality in ad-

TABLE IV Predictors of Cardiac Mortality in 637 Patients with Multivessel Disease Undergoing Percutaneous Transluminal Coronary Angioplasty

	Percent Cardiac Survival Estimated by Kaplan-Meier Method*				
Variable No. at Risk	1 Year (n = 509)	3 Years (n = 307)	5 Years (n = 62)	Improvement (Chi-Square)	p Value
Immediate outcome of PTCA					
Successful	96 ± 1	92 ± 1	88 ± 2	11.9[†]	<0.001
Failed	82 ± 4	80 ± 4	77 ± 5		
Left ventricular contraction score ≥12:					
Yes	95 ± 1	92 ± 1	89 ± 2	23.8	<0.001
No	78 ± 6	64 ± 7	59 ± 8		
Diabetes mellitus					
Yes	87 ± 3	82 ± 4	72 ± 9	9.8	0.002
No	95 ± 1	93 ± 1	90 ± 2		
Age ≥65 years					
Yes	90 ± 2	84 ± 3	79 ± 5	8.2	0.004
No	95 ± 1	93 ± 1	90 ± 2		

* Survival estimate ± standard error of the estimate.
[†] Global chi-square.

dition to the immediate outcome of PTCA (successful or failed). Estimated ratio of risks for each of these variables are listed in Table V.

When the analysis was repeated in the group of patients with clinically successful PTCA results, the only significant independent predictor of cardiac mortality was a left ventricular contraction score of ≥12, with an estimated relative risk ratio of 6.2 ($p < 0.001$).

DISCUSSION

In this large consecutive series of patients with multivessel CAD undergoing PTCA (including unsuccessful procedures), the estimated 5-year survival was approximately 90%. There was a relatively stable and low yearly attrition rate of 1 to 2% beyond the first year after PTCA. Because of the selection criteria applied, it is difficult to compare the survival in this series to previously published survival of surgical or medical series.

There is an increased procedural risk of death in patients with multivessel CAD undergoing PTCA. Ellis et al,[13] in a large series of patients, found the presence of multivessel CAD to be a significant independent predictor of in-hospital mortality. Similarly, the National Heart, Lung, and Blood Institute PTCA Registry reported a higher in-hospital mortality in patients with multivessel CAD than in those with 1-vessel disease.[14]

In the current study, failed PTCA was associated with lower survival, mostly because of higher early mortality (Figure 1). We were also able to identify additional risk factors for increased mortality independent of clinical success of the procedure. The presence of these risk factors will increase the likelihood of death should PTCA fail. Among the variables analyzed, old age and the presence of diabetes mellitus were significant clinical predictors of mortality after PTCA. The risk of PTCA has been reported to be increased in elderly pa-

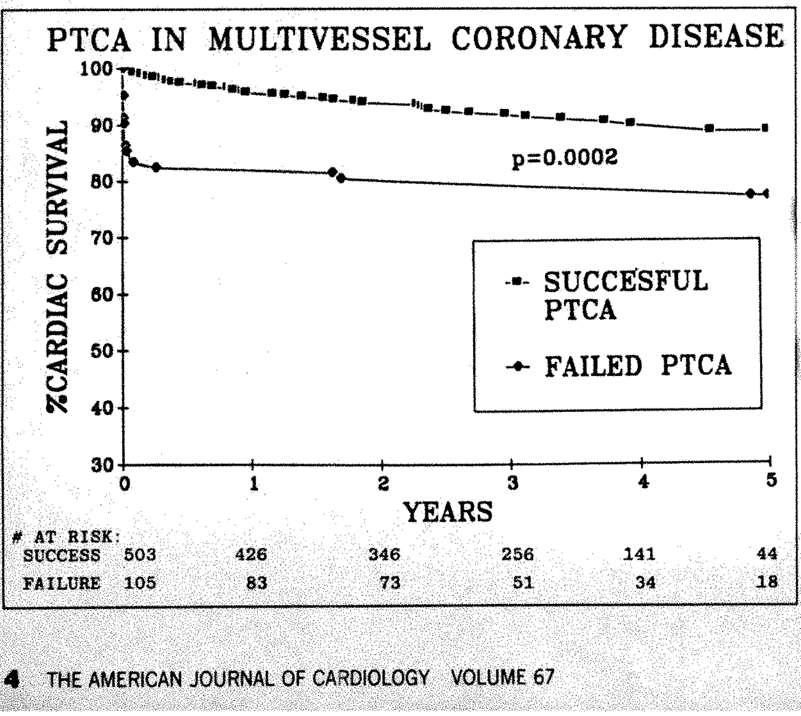

FIGURE 1. Kaplan-Meier 5-year survival curves for patients with multivessel coronary artery disease with successful and failed percutaneous transluminal coronary angioplasty (PTCA). The numbers of patients at risk in each group at each time interval are given at the *bottom* of the figure.

tients.[15] Age is also a known predictor of mortality and morbidity after coronary bypass surgery.[16] The relation of diabetes mellitus to increased risk of mortality after PTCA has also been noted previously.[13] Diabetes mellitus is a well known risk factor for restenosis after PTCA.[17,18] The presence of diabetes is generally associated with a poorer outcome in patients with CAD[19] or in those undergoing coronary artery bypass grafting.[20]

Importance of left ventricular dysfunction as a predictor of mortality: In the overall series of patients undergoing PTCA for multivessel CAD, the presence of left ventricular dysfunction was the most important predictor of mortality (Figure 2, Tables IV and V). The negative impact of left ventricular dysfunction on survival persisted after successful PTCA: The estimated 5-year survival in patients with and without left ventricular dysfunction was 90 ± 2 and 64 ± 10%, respectively ($p < 0.0001$). When the survival was analyzed by Cox regression in the group of patients who had clinical success, the only factor associated with poor long-term outcome was the presence of left ventricular dysfunction. Although left ventricular dysfunction was a strong predictor of cardiac mortality, it was present only in 9% of the patients, presumably because of the clinical selection process for PTCA. The importance of left ventricular function as a predictor of the natural history of CAD[21] and of clinical outcome with medical[10] or surgical[16] therapy is well known.

TABLE V Estimated Relative Risk Ratios for Independent Variables*

Independent Variable	Relative Risk	Ratio of Risks
Immediate outcome of PTCA		
Failed	1.74	1.96
Successful	0.89	
Left ventricular contraction score		
≥12	4.1	4.65
<12	0.88	
Diabetes mellitus		
Present	2.04	2.43
Absent	0.84	
Age (years)		
70	1.47	2.07
50	0.71	

* See Table IV.
PTCA = percutaneous transluminal coronary angioplasty.

Certain subsets of patients with multivessel coronary disease and decreased left ventricular function have demonstrated a survival benefit with surgical revascularization compared with medical therapy.[22] Our study does not provide data on the effect of PTCA compared with medical treatment on survival in patients with left ventricular dysfunction because there is no control group. It is also difficult to make meaningful comparisons of survival with previous studies owing to the different selection criteria applied. In the Coronary Artery Surgery Study, the 7-year mortality rate in patients with multivessel disease who had only mild angina and a left ventricular ejection fraction ≥34% but <50% was 84% for surgically treated and 70% for medically treated patients.[22] The difference between medically and surgically treated patients was only significant in those with 3-vessel disease (65 vs 88%). The important question is whether PTCA in patients with multivessel disease and left ventricular dysfunction would provide a similar survival benefit to that expected from surgical revascularization. In patients with left ventricular regional wall motion abnormalities before PTCA, we observed that regional systolic function was more likely to improve in patients without restenosis.[23] Therefore, it is possible that restenosis may offset some of the possible survival benefit gained by PTCA revascularization.

The effect of the baseline extent of CAD, classified as 2- or 3-vessel CAD according to the usual clinical terminology, on cardiac survival after PTCA for multivessel CAD has not been well defined. Although the natural history of patients with 3-vessel CAD is charac-

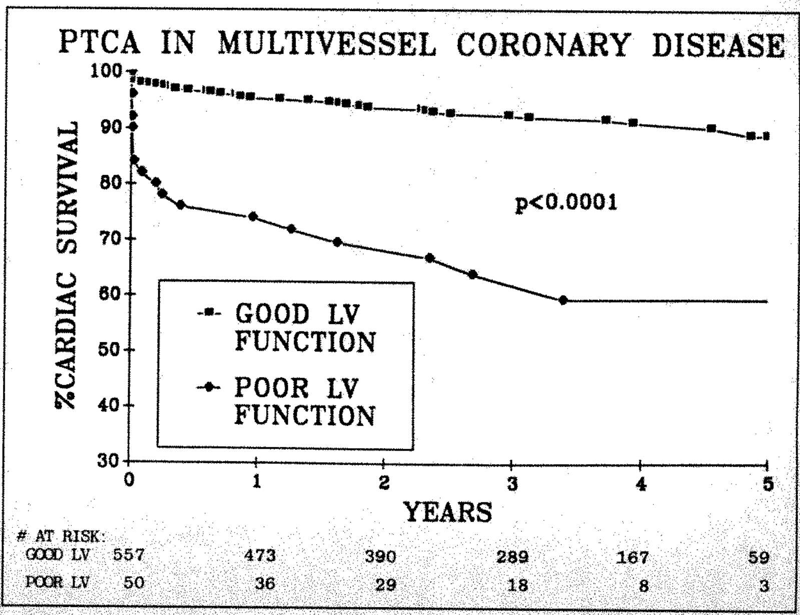

FIGURE 2. Kaplan-Meier 5-year survival curves for patients with multivessel coronary artery disease with left ventricular (LV) contraction score ≥12 (poor LV function) and <12 (good LV function). The numbers of patients at risk in each group at each time interval are given at the *bottom* of the figure. The left ventriculogram was missing in 1 patient.

terized by a lower survival than in those with 2-vessel CAD,[10] the selection process for PTCA probably excludes patients with 3-vessel CAD with worse prognostic characteristics, thus creating a bias toward a similar survival after PTCA in patients with 2- and 3-vessel CAD. The routine clinical "2- or 3-vessel CAD" stratification probably is not a satisfactory method to classify the severity of CAD in patients undergoing PTCA. A myocardial jeopardy score based on the size of territory supplied by each vessel may have more prognostic value.[24] The degree of revascularization (complete versus incomplete) obtained with PTCA was not a predictor of survival in our study. The follow-up data from the National Heart, Lung, and Blood Institute PTCA Registry[25] showed that patients with incomplete revascularization had a higher mortality, with an estimated risk of 1.63, than those with complete revascularization. However, when a logistic regression model was used to adjust for significant differences in baseline, including an ejection fraction <50%, the adjusted estimate of risk of death was no longer different between patients with incomplete and complete revascularization.

Clinical implications: Our study indicates that in patients with multivessel CAD who undergo PTCA, left ventricular function is the most important determinant of cardiac survival, independent of the immediate success or failure of PTCA. Old age and diabetes mellitus were also important when failed and successful PTCA cases were analyzed together. These results may provide important clinical guidelines for selecting patients with multivessel CAD for PTCA. In future studies evaluating long-term outcome after PTCA, the effects of these variables must be taken into consideration.

Acknowledgment: We wish to thank the J. Gerard Mudd Cardiac Catheterization Team and Donna Sander for manuscript preparation.

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Outcomes of Direct Coronary Angioplasty for Acute Myocardial Infarction in Candidates and Non-Candidates for Thrombolytic Therapy

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Coronary angioplasty without prior thrombolytic therapy was performed in 383 patients with acute myocardial infarction (AMI). Patients were divided into 2 groups depending on whether they were candidates or non-candidates for thrombolytic therapy. Patients were not considered thrombolytic candidates if they: (1) presented in cardiogenic shock, (2) were ≥75 years of age, (3) had had coronary artery bypass surgery or, (4) had a reperfusion time of >6 hours. Thrombolytic and nonthrombolytic candidates had similar rates of reperfusion (92 vs 88%), nonfatal reinfarction (6.0 vs 5.9%) and recurrent myocardial ischemia (1.8 vs 0%). Thrombolytic candidates had a lower mortality rate (3.9 vs 24%, p <0.0001) and a lower incidence of bleeding (4.6 vs 10.9%, p <0.05). Improvement in left ventricular ejection fraction at follow-up angiography was 4.4% in thrombolytic and 10.5% in nonthrombolytic candidates (p <0.002). Ejection fraction improved most in patients with anterior wall AMI (7.7% in thrombolytic candidates, 15.1% in nonthrombolytic candidates) and in patients with reperfusion times >6 hours (14.2%).

These outcomes suggest that direct coronary angioplasty is a viable alternative method of reperfusion in patients with AMI who are candidates for thrombolytic therapy. Nonthrombolytic candidates are a high-risk group of patients. Direct coronary angioplasty may be beneficial in certain subgroups, especially for patients in cardiogenic shock and for patients presenting >6 hours after the onset of chest pain with evidence of ongoing ischemia.

(Am J Cardiol 1991;67:7–12)

It is now well established that coronary artery reperfusion is beneficial in the early treatment of acute myocardial infarction (AMI).[1-3] Intravenous thrombolytic therapy is the most widely used method of reperfusion, but is limited by modest reperfusion rates, significant residual stenosis of the infarct vessel and contraindications to its use in many patients. Percutaneous transluminal coronary angioplasty has been used in an attempt to overcome these limitations, but the results of several large multicenter trials suggest that routine angioplasty after thrombolytic therapy may have limited value.[4-7]

Direct coronary angioplasty without prior thrombolytic therapy has been used to establish reperfusion in patients with AMI, but its role has remained controversial.[8-10] Most published studies have been small and have not allowed analysis of subsets of patients, and this has made comparisons with other reperfusion strategies difficult.[8,9,11-14] This study evaluates the role of direct angioplasty in the treatment of AMI in 2 major subgroups of patients—patients who are considered candidates and patients who are considered not to be candidates for thrombolytic therapy.

METHODS

Study patients: The study population comprised 383 consecutive patients with transmural AMI treated with primary coronary angioplasty, without prior thrombolytic therapy, at The Moses Cone Memorial Hospital from 1984 through 1988. An electrocardiographic ST-segment elevation of ≥1 mm in ≥2 contiguous leads was required. Patients presenting with chest pain after 4 to 6 hours were selected only if they had evidence of ongoing ischemia or hemodynamic compromise. During the study period, 636 patients with AMI were treated by our cardiology group. Of these patients, 201 were not treated with reperfusion therapy because they did not meet electrocardiographic criteria for transmural AMI, presented late after the onset of chest pain, or had severe disease of other organ systems. Twenty-seven patients were treated with primary thrombolytic therapy, which was often given before referral to our institution. Twenty-five patients had emergency catheterization, but did not have coronary angioplasty because the infarct vessel was small or because the anatomy was unfavorable for angioplasty. The remaining 383 patients treated with direct angioplasty comprised our study group.

From the Department of Medicine, The Moses H. Cone Memorial Hospital, Greensboro, North Carolina. This work was supported by a grant from the Education Committee, The Moses H. Cone Memorial Hospital, Greensboro, North Carolina, and by a grant from United States Catheters and Instruments division of CR Bard, Inc., Billerica, Massachusetts. Manuscript received July 2, 1990; revised manuscript received and accepted August 28, 1990.

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Patient subgroups: Patients were classified into 2 major subgroups depending on whether they met generally accepted criteria for inclusion in thrombolytic trials.[4,7] Patients were considered nonthrombolytic candidates if they: (1) presented in cardiogenic shock, (2) were ≥75 years of age, (3) had undergone coronary artery bypass graft surgery, or (4) had a reperfusion time of >6 hours. All other patients were considered thrombolytic candidates. These criteria are those used in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial and are similar to criteria used in the Thrombolysis in Myocardial Infarction (TIMI) II-B trial, although the TIMI-II-B trial included a small number of patients with cardiogenic shock.[4,7,15]

Treatment protocol: Patients with AMI were given sublingual and intravenous nitroglycerin, intravenous heparin (5,000 U) and lidocaine in the emergency room and were transported promptly to the cardiovascular laboratory. An experienced cardiac catheterization team consisting of 3 technicians and 1 or 2 invasive cardiologists was on call 24 hours a day and the procedure generally could be started within 30 to 60 minutes of notification. Coronary angiography and left ventriculography were performed by the femoral approach. The infarct vessel was identified, reperfusion was established mechanically with a guidewire, and coronary angioplasty was performed using standard techniques. In patients in cardiogenic shock, an intraaortic balloon was frequently inserted. All patients received 12,000 to 20,000 U heparin during the procedure and a heparin infusion for 4 to 6 days to keep the partial thromboplastin time 2 to 3 times the control. Unless contraindicated, all patients received enteric-coated aspirin, intravenous nitroglycerin, calcium channel blockers and β blockers after the procedure. Aspirin was not given routinely before the procedure until the last few months of the study period.

Definitions: Cardiogenic shock was defined as hypotension (systolic blood pressure <85 mm Hg) not responsive to volume expansion and associated with severe left ventricular dysfunction or severe right ventricular infarction. Reperfusion time was the time from the onset of chest pain until mechanical reperfusion was established with the angioplasty wire. Successful angioplasty was defined as successful reperfusion with reduction in the luminal diameter stenosis to ≤60%. Reinfarction was defined as recurrent ischemic chest pain associated with new or worse ST-segment elevation, or a new rise in creatine kinase and the MB fraction, or both. Recurrent ischemia was defined as recurrent ischemic chest pain, without criteria for infarction, requiring intervention with either repeat coronary angioplasty or coronary bypass graft surgery.

Follow-up catheterization and angiography: Follow-up angiography was performed routinely at 6 months in consenting patients during the first 3 years of the study but was performed only when clinically indicated during the last 2 years. Follow-up studies were obtained in 81% of survivors during the first 3 years and in 63% of survivors during the entire study period. Left ventricular ejection fractions were calculated from tracing contours of right anterior oblique ventriculograms using the area-length method with correction for the 30° right anterior oblique projection.[16] Only sinus beats were analyzed, and ventriculograms were omitted if opacification was inadequate. Observers were blinded as to whether the ventriculograms were from acute or follow-up studies and whether the infarct vessel was patent or occluded.

Data analysis: Chi-square with Yates' correction for continuity was used as a test of the homogeneity of proportions for analyses involving pairs of dichotomous variables. Fisher's 2-tailed exact probabilities were calculated for all fourfold tables when ≥1 of the expected cell frequencies was <5. Student's *t* test for independent samples was used to analyze the difference in means of continuous variables. Values are expressed as mean ± 1 standard deviation. Multiple logistic regression was used to assess the relations between baseline variables and hospital mortality.

RESULTS

Baseline characteristics (Table I): As expected from the selection criteria, nonthrombolytic candidates were older and had longer reperfusion times than thrombolytic candidates. Nonthrombolytic candidates also included a greater number of female patients, had a greater incidence of previous myocardial infarction and multivessel coronary disease, and had a lower initial left ventricular ejection fraction than thrombolytic candidates.

Hospital outcomes (Table II): Successful angioplasty was performed in 92% of thrombolytic and in 88% of nonthrombolytic candidates. Hospital mortality was significantly lower in thrombolytic than in nonthrombolytic candidates (3.9 vs 24%, p <0.0001). Nonfatal reinfarction was similar in both groups. Fourteen of the 23 patients with reinfarction had repeat emergency angioplasty and 12 of these were successful. Recurrent ischemia requiring intervention occurred in 5 (1.8%) thrombolytic and in none of the nonthrombolytic candidates. Coronary artery bypass surgery during the hospital stay was required in 18 (6.4%) thrombolytic and in 8 (7.9%) nonthrombolytic candidates. This includes emergency bypass surgery after failed angioplasty in 3 (1.1%) thrombolytic and in 2 (2.0%) nonthrombolytic candidates, and urgent bypass surgery for recurrent ischemia in 3 (1.1%) thrombolytic candidates. In most cases, coronary artery bypass surgery was performed electively for left main or multivessel disease. Bleeding occurred more frequently in nonthrombolytic candidates. There were no patients who developed intracranial hemorrhage.

Variables related to hospital mortality (Table III): In the entire cohort of 383 patients, there were 5 positive independent predictors of mortality by multivariate analysis. These were unsuccessful angioplasty, cardiogenic shock, age ≥75 years, reperfusion time >6 hours and multivessel coronary disease. All 4 criteria used to define nonthrombolytic candidates had high mortality and 3 were positive independent predictors of mortality.

Outcomes in subgroups of nonthrombolytic candidates (Table IV): Patients presenting with cardiogenic

TABLE I Baseline Characteristics of 383 Patients Treated with Direct Angioplasty

Characteristic	Thrombolytic Candidates (n = 282) No. (%)	Nonthrombolytic Candidates (n = 101) No. (%)	p Value
Age (yrs)	57 ± 10	65 ± 13	NA
Gender (male)	215 (76)	62 (61)	0.005
Prior myocardial infarction	50 (18)	35 (35)	0.0008
Infarct-related coronary artery			
Left anterior descending	119 (42)	53 (53)	0.09*
Right	129 (46)	27 (27)	
Left circumflex	34 (12)	13 (13)	
Vein graft	0 (0)	8 (8)	
Multivessel CAD[†]	141 (50)	63 (62)	0.04
Patent infarct vessel on initial angiogram (TIMI flow grade 2 or 3)	61 (22)	25 (25)	NS
Initial ejection fraction	53.5 ± 12.6	48.4 ± 15.6	0.008
Reperfusion time (hrs)	3.2 ± 1.2	6.4 ± 5.3	NA

* Compares left anterior descending artery with all other vessels; [†] >70% stenosis in 2 or 3 major epicardial vessels; [‡] includes all patients with adequate initial ventriculograms: n = 248 for thrombolytic candidates, n = 82 for nonthrombolytic candidates.

CAD = coronary artery disease; NA = not applicable (variable was used to define nonthrombolytic candidates); NS = not significant; TIMI = Thrombolysis in Myocardial Infarction trial.

shock had a lower reperfusion rate and a higher mortality rate than thrombolytic candidates. There were no patients with reinfarction or recurrent ischemia, but coronary bypass surgery was required more frequently than in thrombolytic candidates. Patients ≥75 years of age had a high reperfusion rate. However, mortality rate, incidence of nonfatal reinfarction and incidence of bleeding were significantly higher than for thrombolytic candidates. Patients with prior coronary artery bypass graft surgery had a lower reperfusion rate and a higher mortality rate than thrombolytic candidates. Angioplasty was successful in 5 of 8 patients whose infarct vessel was an occluded vein graft, but 2 developed reinfarction and 2 required repeat bypass surgery. Patients with reperfusion times >6 hours had a high reperfusion rate, a low incidence of reinfarction and no recurrent ischemia. The hospital mortality rate was high compared with that of thrombolytic candidates, but these patients were selected partly because of hemodynamic compromise. The mortality rate in nonthrombolytic candidates, excluding patients in cardiogenic shock, was 13 of 79 (16%).

Cardiac catheterization laboratory complications: Laboratory death occurred in 7 (6.9%) nonthrombolytic and in 3 (1.1%) thrombolytic candidates ($p < 0.004$). Most of the deaths in the nonthrombolytic group (6 of 7) occurred in patients in cardiogenic shock or ≥75 years of age. Ventricular fibrillation occurred in 16 (15.8%) nonthrombolytic and in 24 (8.5%) thrombolytic candidates ($p = 0.06$). Prolonged cardiopulmonary resuscitation was required in 13 (12.9%) nonthrombolytic and in 9 (3.2%) thrombolytic candidates ($p < 0.001$). There was 1 procedure-related stroke believed to be due to an embolus. Most of the major complications (5 of 10 laboratory deaths and 3 of 5 emergency bypass operations) occurred early in our experience (first 100 patients) with direct angioplasty.

Improvement in left ventricular ejection fraction (Table V): Follow-up angiography was performed in 63% of survivors at a mean follow-up time of 8 months. Long-term patency of the infarct-related artery was 85%. Adequate paired ventriculograms for measurement of ejection fractions were achieved in 53% of survivors.

Nonthrombolytic candidates had lower initial ejection fractions and a greater improvement in ejection fraction than thrombolytic candidates. The final ejection fraction was well preserved in both groups. Patients with anterior infarctions had lower initial ejection fractions and greater improvement in ejection fraction than patients with inferior and posterior infarctions.

In patients with adequate paired ventriculograms, the mean improvement in ejection fraction was 7.9 ± 8.1% in 7 patients in cardiogenic shock, 7.3 ± 11.2% in 6 patients ≥75 years of age and 14.2 ± 9.4% in 20 patients with reperfusion times >6 hours.

DISCUSSION

This study evaluates the role of direct angioplasty in the treatment of AMI. By separating our patients into 2 major subgroups, depending on whether they were considered candidates or non-candidates for thrombolytic therapy, we were able to obtain a study population of

TABLE II Hospital Outcomes of 383 Patients Treated with Direct Angioplasty

Outcome	Thrombolytic Candidates (n = 282) No. (%)	Nonthrombolytic Candidates (n = 101) No. (%)	p Value
Successful PTCA	258 (91.5)	89 (88.1)	NS
Hospital mortality	11 (3.9)	24 (23.7)	0.0001
Nonfatal reinfarction	17 (6.0)	6 (5.9)	NS
Recurrent ischemia	5 (1.8)	0 (0.0)	NS
CABG	18 (6.4)	8 (7.9)	NS
Bleeding*	13 (4.6)	11 (10.9)	0.05

* Requiring transfusion of ≥2 units of blood, excluding patients who had coronary bypass surgery.

CABG = coronary artery bypass grafting; NS = not significant ($p > 0.10$); PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Variables Related to Hospital Mortality in All 383 Patients Treated with Direct Angioplasty

Variable	No. of Pts.	Mortality Rate No. (%)	Multivariate Analysis Odds Ratio	95% CI
Unsuccessful PTCA	36	14 (39)	3.38	2.00–5.72
Cardiogenic shock	22	11 (50)	3.23	1.77–5.89
Age ≥75 years	30	9 (30)	3.10	1.73–5.54
Reperfusion time >6 hours	48	8 (17)	2.15	1.26–3.68
Multivessel CAD	204	29 (14)	1.89	1.12–3.19
Prior CABG	12	3 (25)	1.40	0.58–3.40
Anterior wall infarction	172	21 (12)	1.37	0.88–2.16
Female gender	106	13 (12)	1.25	0.78–2.00
Prior myocardial infarction	85	14 (17)	1.21	0.74–1.96

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; PTCA = percutaneous transluminal coronary angioplasty.

TABLE IV Outcomes After Direct Angioplasty in Subgroups of Nonthrombolytic Candidates

Outcome	Cardiogenic Shock (n = 22) No. (%)	Age ≥75 Years (n = 30) No. (%)	Prior CABG (n = 12) No. (%)	Reperfusion Time >6 Hours (n = 48) No. (%)
Successful PTCA	15 (68)‡	27 (90)	9 (75)	46 (96)
Hospital mortality	11 (50)§	9 (30)§	3 (25)†	8 (17)‡
Nonfatal reinfarction	0 (0)	6 (20)†	1 (8)	2 (4)
Recurrent ischemia	0 (0)	0 (0)	0 (0)	0 (0)
CABG	3 (14)	2 (7)	2 (17)	3 (6)
Bleeding*	3 (13)	5 (17)†	2 (17)	2 (4)

* Requiring transfusion of ≥2 units of blood, excluding patients who had coronary bypass surgery; † $p < 0.05$ (compares each subgroup of nonthrombolytic candidates with thrombolytic candidates); ‡ $p < 0.01$; § $p < 0.001$.

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

thrombolytic candidates comparable to the 2 major North American thrombolytic trials.[4,7] Our results suggest that in patients who are candidates for thrombolytic therapy, the outcomes after direct angioplasty compare very favorably to the outcomes after intravenous thrombolytic therapy or a combination of intravenous thrombolytic therapy and angioplasty.

Hospital outcomes in thrombolytic candidates: Our patency rate of 92% with direct angioplasty is higher than patency rates with intravenous streptokinase (41 to 55%) or standard doses of intravenous tissue plasminogen activator (75%).[17,18,4] High patency rates have recently been reported with rapid- or high-dose tissue plasminogen activator infusion protocols, but these may be associated with an increased risk of bleeding.[19,20]

The hospital mortality rate in our thrombolytic candidates of 3.9% compares favorably with the 7% mortality rate in the TAMI trial and with the 4.7% mortality rate in the TIMI-II-B trial.[4,7] O'Keefe et al[10] also reported a very low hospital mortality rate in thrombolytic candidates treated with direct angioplasty.

The incidence of nonfatal reinfarction in our thrombolytic candidates is similar to the 5.6% incidence in the TIMI-II-B study and suggests that direct angioplasty offers no advantage in the prevention of nonfatal reinfarction.[7]

The incidence of recurrent ischemia was only 1.8% in our patients treated with direct angioplasty. This is in striking contrast to the high incidence of recurrent ischemia in the TAMI study (18%) and in the TIMI-II-B study (25%).[4,7] Part of these differences may be related

TABLE V Improvement in Left Ventricular Ejection Fraction in Survivors After Direct Angioplasty

	Ejection Fraction Initial (%)	Final (%)	Improvement (%)
Thrombolytic candidates (n = 149)	53.3 ± 12.6	57.7 ± 13.1	4.4 ± 10.4
Nonthrombolytic candidates (n = 36)	47.8 ± 13.1	58.3 ± 11.6	10.5 ± 9.9
p Value	0.03	NS	0.002
Thrombolytic candidates			
Anterior wall infarction (n = 69)	47.1 ± 12.5	54.8 ± 15.1	7.7 ± 10.9
Inferior and posterior infarction (n = 80)	58.7 ± 10.0	60.3 ± 10.4	1.6 ± 9.2
p Value	0.001	0.02	0.0003
Nonthrombolytic candidates			
Anterior wall infarction (n = 22)	41.8 ± 7.7	56.9 ± 9.2	15.1 ± 8.5
Inferior and posterior infarction (n = 12)	57.4 ± 13.3	61.9 ± 12.1	4.5 ± 7.3
p Value	0.002	NS	0.0009

n = number of patients with adequate paired ventriculograms; NS = not significant.

to study design and definitions. The TAMI study included nonfatal reinfarction in the recurrent ischemia group and the TIMI-II-B study provoked ischemia with stress testing before hospital discharge and at 6 weeks. Despite these differences, the incidence of recurrent ischemia with direct angioplasty is very low compared with that of other strategies.

Our incidence of bleeding (4.6%) is similar to the incidence of bleeding from intravenous thrombolytic therapy alone (4.3%) and is substantially lower than the incidence of bleeding when intravenous thrombolytic therapy is combined with invasive procedures (21%).[4,7] The major catastrophic complication of intravenous thrombolytic therapy—intracerebral hemorrhage, which occurs in approximately 0.5% of patients treated with intravenous tissue plasminogen activator[4,7]—did not occur in our study and has not been reported in other series of patients treated with direct angioplasty.[8-10]

We were able to document a 4.4% improvement in left ventricular ejection fraction at follow-up angiography in thrombolytic candidates and a 7.7% improvement in patients with anterior infarctions. This contrasts with 1.2% improvement in ejection fraction in the TAMI study.[4] Other studies with direct angioplasty, including 1 controlled study comparing direct angioplasty with intracoronary streptokinase, have shown substantial improvement in ejection fraction at follow-up angiography.[8,21] This suggests that direct angioplasty may have an advantage over other reperfusion strategies in the preservation of left ventricular function.

Hospital outcomes in nonthrombolytic candidates: The baseline characteristics and hospital outcomes of our nonthrombolytic candidates suggest that they are a high-risk subgroup compared to thrombolytic candidates. Nonthrombolytic candidates were older, included a greater number of women, had a greater incidence of previous myocardial infarction and multivessel coronary disease, and had a lower initial ejection fraction than thrombolytic candidates.

Patients presenting in cardiogenic shock comprise the subgroup at highest risk. Hospital mortality rates with conventional therapy have been 73 to 83%.[22,23] With thrombolytic therapy, reperfusion rates have been low (43%) and mortality rates have remained relatively high (67 to 70%).[2,24] Our reperfusion rate of 68% and our hospital mortality rate of 50% compare very favorably with this. Other investigators have reported similar reperfusion and mortality rates with direct angioplasty and have advocated this approach in the treatment of AMI complicated by cardiogenic shock.[10,23]

Patients ≥75 years of age also are a very high-risk subgroup. In these patients, direct angioplasty resulted in a high patency rate and good improvement in ejection fraction, but was associated with a high incidence of bleeding and reinfarction and a high mortality rate. Thrombolytic therapy has frequently been avoided in elderly patients because of the increased risk of bleeding complications, but data from the second International Study of Infarct Survival (ISIS) trial suggest that these patients may benefit.[3] It is not clear from our data which is the best therapeutic approach in these patients.

In our patients with prior coronary artery bypass grafting, the reperfusion rate with direct angioplasty was lower than it was for thrombolytic candidates because of a lower rate of reperfusion in occluded vein grafts. Occluded vein grafts also have an increased chance of reocclusion after successful angioplasty. Despite these limitations, others have suggested that angioplasty may be preferential to intravenous thrombolytic therapy in this group of patients.[25,26] The number of patients with prior bypass surgery in our series is small, and we cannot draw any conclusions regarding the potential benefit of direct angioplasty.

Patients with reperfusion times >6 hours treated with direct angioplasty had a high reperfusion rate and substantial improvement in left ventricular ejection fraction. The marked improvement in ejection fraction is unexpected with late reperfusion and may be related to the selection criteria. These patients were selected in part because of persistent chest pain and evidence of ongoing ischemia, which may be an indication of continued myocardial viability. The relatively high mortality rate in this group of patients also may be related to the selection criteria. Patients were selected for intervention after 6 hours of chest pain partly because of evidence of hemodynamic compromise. If patients in cardiogenic shock and with pulmonary edema, and patients ≥75 years are excluded, the hospital mortality rate is 2.5% in this group of patients. These data suggest that in patients who present late after the onset of chest pain, but who have evidence of ongoing ischemia, direct angioplasty may offer substantial benefit.

Limitations of direct angioplasty: Direct angioplasty has several limitations as a reperfusion strategy. Only about 12% of hospitals in the United States have angioplasty facilities and not all of these are equipped to perform emergency angioplasty.[27] There is time-delay in mobilizing the catheterization laboratory team and in establishing coronary reperfusion with direct angioplasty, although in our institution this delay is small. Direct angioplasty is also associated with risks as demonstrated by our laboratory complications. Most of these complications occurred early in our series, suggesting that experience is important in minimizing complications with this approach. Fortunately, the risk of complications appears small, especially in thrombolytic candidates, and our overall results suggest that the benefits outweigh the risks.

Study limitations: Our study is limited by the lack of a concurrent randomly selected control group of patients treated by another reperfusion strategy. We cannot exclude the possibility that the outcomes observed in our patients were produced by selection bias. The observations made by others—that direct angioplasty is associated with favorable hospital outcomes in thrombolytic candidates—support the hypothesis that these results occurred because of therapeutic benefit.[10]

Our data regarding the improvement in left ventricular ejection fraction after direct angioplasty are based on follow-up studies in 53% of survivors. Extrapolation to the entire population is subject to possible error. However, our results in the first 3 years of the study, when follow-up angiography was available in 81% of survivors, were similar to the entire group, and suggest that the improvement in ejection fraction is representative of the entire population.

Acknowledgment: We thank the technical staff of the cardiovascular laboratory at The Moses H. Cone Memorial Hospital for their invaluable help with these patients, Mike Duran, PAC, Michelle Mullaney, PAC, and Ken Hampton for their help in processing the data, and Susan Welborn for secretarial assistance.

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Severity of Single-Vessel Coronary Arterial Stenosis and Duration of Angina as Determinants of Recruitable Collateral Vessels During Balloon Angioplasty Occlusion

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To determine the factors that influence the presence of collateral vessels during coronary occlusion, we performed standardized contrast injection of the contralateral coronary artery in 58 consecutive patients, without previous myocardial infarction, undergoing percutaneous transluminal coronary angioplasty for 1-vessel disease (left anterior descending artery in 45, right coronary artery: in 10 and left circumflex artery in 3). The presence of collateral vessels during coronary occlusion, defined as partial or complete epicardial opacification by collateral vessels of the vessel dilated, was related to clinical, angiographic and electrocardiographic parameters. The angiographic appearance of collateral vessels during balloon inflation showed a weak, although statistically significant, correlation to the percent diameter stenosis before angioplasty ($r = 0.28$; $p = 0.03$) and the duration of angina ($r = 0.37$; $p = 0.004$). By combining lesion severity with the duration of angina, collateral vessels during coronary occlusion were particularly related to a lesion severity ≥70% and duration of angina ≥3 months ($p < 0.001$). Furthermore, the presence of collateral vessels was associated with an absence of ST-segment shift (≥1 mm) during 1 minute of coronary occlusion ($p < 0.001$).

(Am J Cardiol 1991;67:13–17)

Numerous studies have documented the protective potential of collateral vessels in acute myocardial infarction.[1] Despite these important observations, there is, however, limited information regarding factors influencing the collateral flow to myocardium at risk in acute coronary syndromes. Percutaneous transluminal coronary angioplasty (PTCA) serves as a unique model to study the collateral circulation in a prospective way. Several studies have demonstrated marked differences in collateral filling using contralateral coronary injection before and during coronary occlusion.[2,3] These so called "recruitable" collateral vessels have shown functional significance and are to be taken into account when the collateral circulation is the subject of study. To identify factors that may influence the development of spontaneously visible and recruitable collateral vessels, we used the PTCA setting to relate the presence of collateral vessels to clinical, angiographic and electrocardiographic parameters.

METHODS

Patients: Fifty-eight consecutive patients (48 men and 10 women, mean age ± standard deviation 57 ± 9 years [range 38 to 79]) with 1-vessel disease, referred to our institution for PTCA, were prospectively studied. Inclusion criteria were (1) angina pectoris refractory to medical therapy without a history of previous myocardial infarction; (2) right dominant coronary circulation; and (3) left ventricular ejection fraction >50%. Exclusion criteria were (1) anemia, renal insufficiency, previous cardiac surgery or previous thrombolytic therapy; (2) electrocardiographic evidence of left ventricular hypertrophy or conduction abnormalities; (3) peripheral artery disease limiting arterial access; (4) multilesion 1-vessel disease or total coronary occlusion. Informed consent was given according to the rules of the Institutional Ethics Committee who approved the study.

Clinical parameters, electrocardiographic and laboratory findings were recorded on admission by the same observer (J.P.). The medical history was verified by a second blinded observer. A third interview followed in case of disagreement on the clinical data and a consensus was reached.

Cardiac catheterization: Therapy with all antianginal medication was continued until cardiac catheterization. In addition, all patients received aspirin (300 mg)

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TABLE I Clinical and Angiographic Data of 58 Patients Before Angioplasty

Age (years)	57 ± 9 (range 38–79)
Gender (male/female)	48/10
Functional class (NYHA III/IV)	25/33
Systemic hypertension (+/0)	10/48
Cigarette smoking (+/0)	36/22
Total cholesterol >250 mg/dl (+/0)	16/42
Diabetes mellitus (+/0)	4/54
Duration of angina (months)	mean 3.3 (range 0.25–12)
Medication	
β blocker (+/0)	48/10
Nitrates (+/0)	38/20
Calcium antagonist (+/0)	48/10
Mean blood pressure (mm Hg)	90 + 12
Coronary artery dilated (LAD/right/LC)	45/10/3
Location of coronary narrowing (proximal/distal)	27/31
Narrowing severity (%diameter ↓)	mean 82 (range 58–99)
Collateral grading	0.4 ± 0.7

LAD = left anterior descending artery; LC = left circumflex artery; NS = not significant; NYHA = New York Heart Association; + = yes; 0 = no.

orally the night before. Lorazepam (3 mg) was orally administered before the procedure. During catheterization all patients received heparin intravenously (i.v.) (5,000 IU) as a bolus. Nifedipine (10 mg) orally and nitroglycerin (0.1 mg i.v.) were given shortly before the first balloon inflation. Continuous administration of nitroprusside (i.v.) was only performed in 8 of the 58 patients with unstable angina to maintain systolic blood pressure at <120 mm Hg. Cardiac catheterization was performed in all patients by percutaneous femoral approach. An 8Fr sheath (USCI) was inserted in both the right and left femoral artery. An 8Fr guiding catheter (Schneider-Shiley) was used for guidance of the balloon catheter (Schneider-Shiley, ACS) and for angiography of the contralateral artery.

Study protocol: Angiography of the contralateral artery was performed before angioplasty by automatic contrast injection (Angiomat 3000, Liebel-Flarsheim Co.; right coronary artery 4 to 6 ml, 7 ml/s; left coronary artery 6 to 8 ml, 9 ml/s). Cineangiography was continued until there was no further opacification of the injected vascular bed. At 30-second balloon inflation, another arteriogram of the contralateral artery was obtained. To determine the reproducibility of the method, additional contralateral injections were performed if >1 dilatation was necessary for successful angioplasty. Angiography of the contralateral artery was repeated after the PTCA procedure. A 12-lead electrocardiogram was recorded throughout the entire procedure. The time of balloon inflation and deflation was marked. The electrocardiographic changes were considered significant if a change in the ST segment of ≥ 1 mm, measured at 80 ms after the J point, occurred in any lead.

Quantitative coronary angiography: Severity of coronary narrowings was determined by measuring the percent reduction in luminal diameter with a digital electronic caliper (Sandhill Scientific, model EC 1) in 2 projections. The measurement was repeated by a second independent angiographer to determine interobserver variability. A stenosis was considered 95% if there was an interruption of contrast medium but complete and brisk filling of the distal part of the stenosed artery, and 99% if there was a slow filling of the distal part. A lesion was considered proximal when it was located in the right coronary artery before the acute marginal branch, in the left circumflex artery before the first marginal branch, and in the left anterior descending artery before the first septal perforator. The collateral vessels were graded as: 0 = no filling of collateral vessels; 1 = filling of collateral vessels to the vessel dilated without any epicardial filling; 2 = partial epicardial filling by collateral vessels of the vessel dilated; and 3 = complete filling by collateral vessels of the vessel dilated. The grading of the collateral vessels was performed independently by 2 angiographers and a consensus was reached in case of disagreement. Collateral vessels were considered absent during coronary occlusion when they were graded 0 or 1 and present when they were graded 2 or 3. Collateral vessels graded 0 and 1 as well as 2 and 3 were combined for the analysis.

Statistics: The relation between the continuous variable age and mean blood pressure (expressed as mean ± standard deviation) and the presence of collateral vessels during coronary occlusion was evaluated with the unpaired Student's t test. The relation between the continuous variable duration of angina and coronary lesion severity and the grading of collateral vessels during coronary occlusion was evaluated with the Spearman rank correlation coefficient. The chi-square test was used for comparing dichotomous variables, coronary lesion severity combined with duration of angina, and signs of ischemia during 1 minute of occlusion. A p value <0.05 was considered statistically significant.

RESULTS

The clinical and angiographic data of the 58 patients are listed in Table I. The PTCA procedure was successfully completed in the 58 patients and adequate coronary angiograms could be obtained in all patients. The angiographic appearance of the collateral vessels during balloon inflation was highly reproducible in all patients who had >1 dilatation performed (56 of the 58 patients). The interobserver variability of the caliper method was 4 ± 6% (mean difference ± standard deviation; $r = 0.69$). At a cutoff point of severity of the coronary lesion $\geq 70\%$, the κ value (proportion of potential agreement beyond chance between 2 observers) was 0.75.[4]

Angiography of collateral vessels before, during and after balloon inflation: Before the first balloon inflation, collateral vessels were grade 0, 42 patients; grade 1, 11; grade 2, 3; and grade 3, 2. During balloon inflation collateral vessels remained absent (grade 0 or 1) in 35 patients and were present (grade 2 or 3) in 23 patients of whom 5 patients had collateral vessels before occlusion. Thus, 18 patients had recruitable collateral vessels. None of the 8 patients with unstable angina had collateral vessels during coronary occlusion. Collateral vessels were fully absent (grade 0) after successful completion of the procedure in all 58 patients.

Relation of collateral vessels during coronary occlusion and clinical, angiographic and electrocardiographic parameters: Collateral vessels during coronary occlusion were related to the duration of angina (Figure 1; r = 0.37, p = 0.004). Twenty-seven of the 31 patients (87%) with <3 months of angina had absence of collateral vessels during coronary occlusion compared with 8 of the 27 patients (29%) with ≥3 months of angina. There was a weak correlation with the severity of the coronary lesion before angioplasty (Figure 2, r = 0.28, p = 0.03). Patients with ≥70% stenosis but a duration of angina <3 months had markedly less collateral vessel development than patients with ≥70% stenosis and duration of angina >3 months (Figure 3, p <0.001). Collateral vessels during coronary occlusion were not related to other clinical or angiographic variables. Electrocardiographic signs of ischemia during coronary occlusion were reduced in the presence of collateral vessels (Table II).

TABLE II Collateral Vessels (CV) During Coronary Occlusion in Relation to Clinical, Angiographic and Electrocardiographic Parameters

	CV Absent (n = 35)		CV Present (n = 23)
Age (years)	57 ± 9	NS	58 ± 8
Gender (male/female)	27/8	NS	21/2
Functional class (NYHA III/IV)	13/22	NS	12/11
Systemic hypertension (+/0)	5/30	NS	5/18
Cigarette smoking (+/0)	21/14	NS	15/8
Total cholesterol >250 mg/dl (+/0)	7/28	NS	9/14
Diabetes mellitus (+/0)	3/32	NS	1/22
Medication			
β blocker (+/0)	29/6	NS	19/4
Nitrates (+/0)	26/9	NS	12/11
Calcium antagonist (+/0)	31/4	NS	17/6
Mean blood pressure (mm Hg)	89 ± 12	NS	91 ± 13
Coronary artery dilated (LAD/right)	28/4	NS	17/6
Location of coronary narrowing (proximal/distal)	13/22	NS	14/9
ST segment (<1 mm/≥1 mm)	3/32	p <0.001	6/17

Abbreviations as in Table I.

DISCUSSION

Both experimental and clinical studies have demonstrated the importance of collateral vessels for salvage of the myocardium at risk in acute myocardial infarction.[5-8] However, there is limited information regarding the factors influencing growth of collateral vessels in humans because most clinical studies are hampered by their retrospective design. A classic study by Rentrop et al[2] showed the dynamic nature of the collateral circulation during brief coronary occlusion during angioplasty. The use of the angioplasty model offers the unique opportunity to study the collateral circulation in a prospective way. This study also revealed the importance of recruitable collateral vessels that were not taken into account in previous clinical studies. The observations of Rentrop were extended in a recent prospective study by Cohen et al.[9] The clinical and angiographic characteristics of 67 patients with 1-vessel disease and normal left ventricular function were related to the angiographic appearance of collateral vessels during balloon inflation. The grading of collateral vessels was highly correlated to the severity of the coronary stenosis. Despite earlier observations in a smaller patient population,[10] the presence of collateral vessels during coronary occlusion did not correlate with the duration of angina.

The results of our study show some differences with Cohen's study that may be related to differences in composition of the patient population. Although the inclusion criteria in both studies were comparable, the pa-

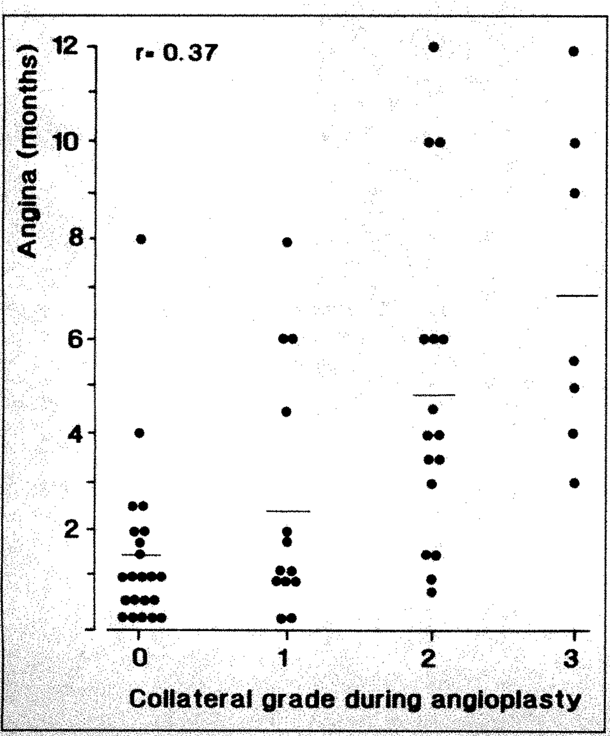

FIGURE 1. Relation between the duration of angina and the collateral grade during balloon inflation in 58 patients.

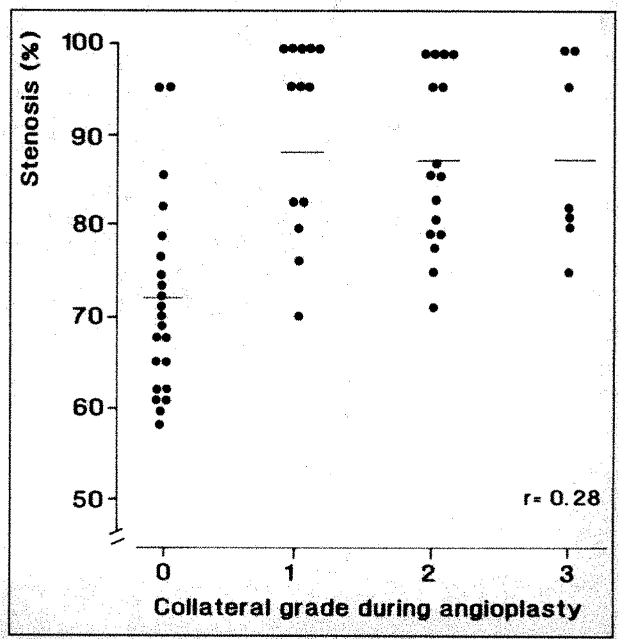

FIGURE 2. Relation between the percent diameter stenosis before angioplasty and the collateral grade during balloon inflation in 58 patients.

tients in their study had a longer period of symptomatic disease, there were more patients with unstable angina and the coronary narrowings were more severe. In addition, there were more patients with proximal lesions and one-third of the patients had disease of the right coronary artery, which was associated in their study with a more extensively developed collateral network. Furthermore, there are also methodologic differences. In our study we used a digital electronic caliper for measurement of the percent diameter stenosis. The accuracy of this method is comparable to computer-assisted systems and superior to the visual estimation of coronary lesion severity.[11] The observed stronger correlation between coronary lesion severity and collateral vessels in Cohen's study can partly be explained by the overestimation of visual measurements with increasing coronary narrowing.[12] In our study, contrast injection of the contralateral vascular bed was performed in a standardized way. These injections were highly reproducible because we could not demonstrate differences in collateral filling in any patient (56 of the 58 patients) in whom >1 balloon inflation was performed. Contrast injection by hand, used in Cohen's study, introduces variations in volume and rapidity of injection which can be critical in the visualization of collateral vascular bed during coronary occlusion. In the present study, epicardial opacification by collateral vessels during 1 minute of coronary occlusion was associated with an absence of electrocardiographic signs of ischemia. This protective potential of collateral vessels confirms the results of other studies[3,10] and indicates that the angiographic assessment of the collateral vascular bed with the injection technique used reflects its function during brief coronary occlusion.

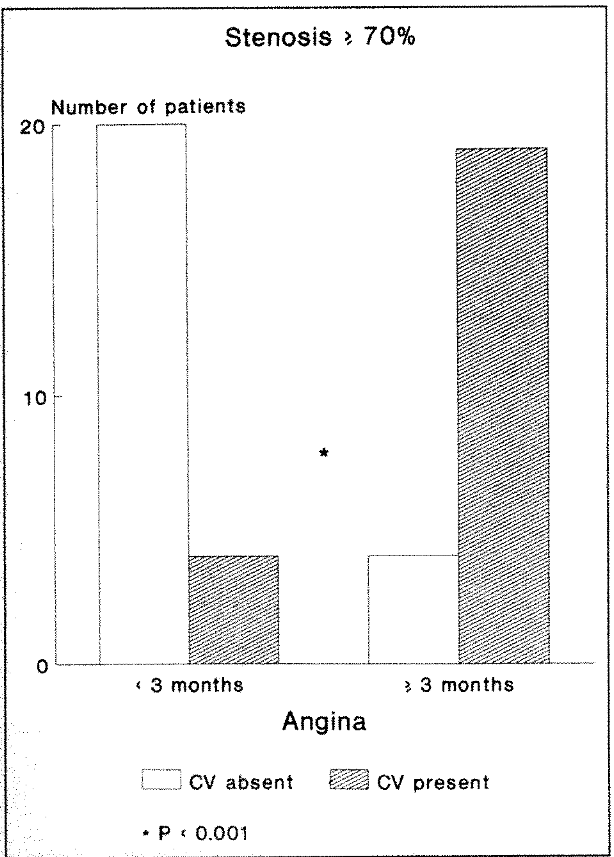

FIGURE 3. Relation between lesion severity ≥70% and duration of angina with the presence or absence of collateral vessels (CV) during coronary occlusion.

Our study included 8 patients with unstable angina who were treated with nitroprusside (i.v.). Administration of nitroglycerin (i.v.) may reduce the resistance of the collateral vascular bed.[13] Collateral vessels, however, were absent during coronary occlusion in all of these patients and therefore it seems unlikely that this has influenced the study results.

The main observation in our study is that the presence of collateral vessels during abrupt coronary occlusion is particularly related to the combination of a coronary lesion severity ≥70% and a duration of ≥3 months of angina (Figure 3). The presence of collateral vessels in more severe coronary lesions is in keeping with experimental and clinical studies demonstrating a threshold of coronary narrowing beyond which there is an increase in collateral flow or angiographic appearance of collateral vessels.[14–17]

The time span necessary for the development of collateral vessels in humans is unknown. In a recent prospective study, Rentrop et al[18] showed that there is a marked increase in angiographic appearance of collateral vessels 10 to 14 days after persistent coronary occlusion in postthrombolytic patients. The present study, which confirms earlier reports, demonstrates the difference in visualization of collateral filling when a maximal or submaximal pressure gradient exists over the collateral vascular bed. Rentrop's angiographic findings are in accordance with experimental data demonstrating a restoration of flow to normal values by collateral vessels within 2 weeks after total coronary occlusion.[19,20] Furthermore, experimental work has demonstrated that the development of the collateral circulation is accelerated when a coronary artery becomes progressively narrowed.[15] By combining clinical and experimental data, the minimal time period for collateral development in subtotal occlusions may likely be >2 weeks and even longer in less severe coronary obstructions.

Our study, as well as Cohen's study, comprised patients with collateral vessels and a short duration of angina (<3 months). One explanation may be that these patients have had coronary narrowings severe enough to stimulate collateral vessel growth in combination with a preceding period of silent ischemia, which is known to occur frequently in coronary artery disease.[21] The data on almost all patients, however, indicate that a period of 3 months of symptomatic disease is required before collateral vessels become angiographically apparent in the presence of obstructive (≥70% stenosis) coronary artery disease.

Study limitations: The results of the study are only applicable to patients with 1-vessel disease and normal left ventricular function since all other patients were excluded. The development of the collateral vascular bed was only assessed by angiography and could not be expressed in terms of flow or resistance. The functional significance of the collateral vessels was judged by electrocardiographic monitoring and was not expanded to hemodynamic monitoring or assessment of global or regional ejection fraction. This study provides only information on the function of collateral vessels during brief coronary occlusion.

Clinical implications: This study indicates that a patient with 1-vessel disease and ≥70% diameter narrowing but with a short duration of angina (<3 months) is unlikely to have developed collateral vessels and is at high risk when a sudden occlusion of the diseased vessel occurs. Consequently, this observation has implications for patient management since priority is usually based on patients' complaints irrespective of the duration.

Acknowledgment: We gratefully acknowledge Rebecca van der Doef, MD, for assistance during the study; Bob van Vlies, MD, for reviewing the manuscript and the Department of Cardiology (head: Albert V.G. Bruschke, MD), Academic Hospital, Leiden, The Netherlands, for their cooperation.

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Characteristics of Black Patients Admitted to Coronary Care Units in Metropolitan Seattle: Results from the Myocardial Infarction Triage and Intervention Registry (MITI)*

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Since 1988, 641 black and 11,892 white patients with chest pain of presumed cardiac origin have been admitted to coronary care units in 19 hospitals in metropolitan Seattle. Black men and women were younger (58 vs 66, p <0.0001), more often admitted to central city hospitals (p <0.0001), and developed evidence of acute myocardial infarction (AMI) less often (19 vs 23%, p = 0.01). In the subset of 2,870 AMI patients, blacks (n = 121) were younger (59 vs 67, p <0.0001) and had less prior coronary artery bypass graft surgery (2 vs 10%, p = 0.005) and more prior hypertension (67 vs 46%, p <0.0001). During hospitalization, whites (n = 2,749) had higher rates of coronary angioplasty (18 vs 10%, p = 0.03) and coronary artery bypass graft surgery (10 vs 4%, p = 0.04), although thrombolytic therapy and cardiac catheterization were used equally in the 2 groups. Hospital mortality was 7.4% for black and 13.1% for white patients (p = 0.07). However, after adjustment for key demographic and clinical variables by logistic regression, this difference was not as apparent (p = 0.38).

Questions about the premature onset of coronary artery disease, excess systemic hypertension, and the differential use of interventions in black persons have been raised by other investigators. Despite differences in age, referral patterns and the use of coronary angioplasty and bypass surgery, black and white patients with AMI in metropolitan Seattle had similar outcomes.

(Am J Cardiol 1991;67:18–23)

The natural history of coronary artery disease and in particular acute myocardial infarction (AMI) in black populations has drawn increasing attention. Several questions have been raised in an attempt to better understand the clinical course of AMI in black patients. First, are black men and women less likely than whites to consult a physician for chest pain and other manifestations of coronary artery disease?[1] Second, is the time from symptom onset to hospital arrival longer for black patients?[2] Third, does the use of therapy for AMI differ according to race?[3–6] Finally, does mortality from AMI and coronary artery disease differ according to race?[7–9]

The objective of this prospective study was to examine the clinical course of black patients with chest pain admitted to coronary care units (CCUs) in metropolitan Seattle, Washington. Specific attention will be given to the subset of patients discharged with the diagnosis of AMI. Black and white populations will be compared according to baseline and clinical features, AMI treatment and outcome.

METHODS

Patient population: From January 1988 to January 1990, 14,283 persons with chest pain were admitted to CCUs in 19 hospitals in King County, which includes the city of Seattle and suburban area with a population of 1.3 million in 1980.[10] Patient hospital records were abstracted, and key information was recorded on study data forms and entered in the Myocardial Infarction Triage and Intervention (MITI) registry.[11] The MITI registry is a randomized trial of prehospital treatment by paramedics of patients with AMI amidst a registry of all patients with AMI. The registry contains all patients who were admitted to CCUs as indicated by CCU logs in 19 hospitals in metropolitan Seattle.

The breakdown of the MITI population by race and AMI status is displayed in Figure 1. The current analysis includes 12,534 patients (87.7%) admitted to CCUs in the metropolitan Seattle area. Patients whose race was unknown (8.6%) or was other than black or white (3.7%) were excluded; 641 black (4.4%) and 11,893 white (83.3%) patients were considered in this analysis. The 2,870 patients with the discharge diagnosis of AMI

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*See Appendix.

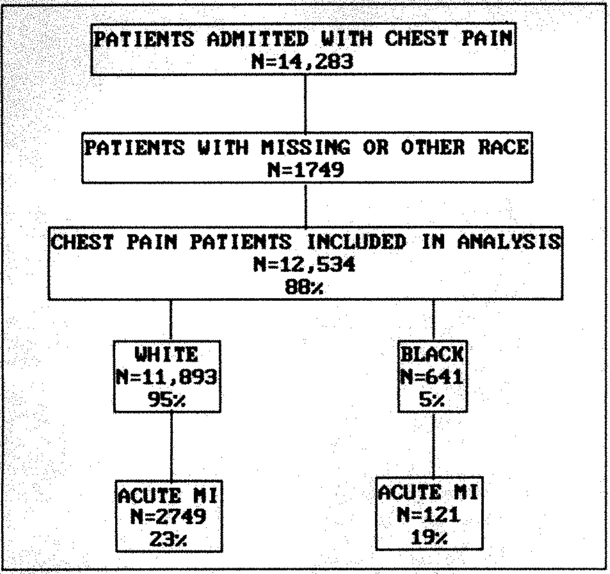
PATIENTS ADMITTED WITH CHEST PAIN
N=14,283
PATIENTS WITH MISSING OR OTHER RACE
N=1749
CHEST PAIN PATIENTS INCLUDED IN ANALYSIS
N=12,534
88%
WHITE
N=11,893
95%
BLACK
N=641
5%
ACUTE MI
N=2749
23%
ACUTE MI
N=121
19%

FIGURE 1. Race and myocardial infarction (MI) status in patients admitted to coronary care units in metropolitan Seattle.

were of particular interest; 19% of black and 23% of white patients had confirmation of AMI at discharge or death.

Study variables: For all patients, basic demographic and diagnostic variables were collected; these included permanent residence, date and hospital of admission, age, gender, race, mode of transport to the hospital, and initial and discharge diagnoses. Race was coded as white, black, Asian/Pacific islander, native American/Alaskan native, Hispanic or unknown. Vital status at hospital discharge and cause of death were indicated.

For those patients with AMI as the discharge diagnosis, additional data were collected. The presence of a series of patient history variables was coded as no/not mentioned, yes, or questionable, and included history of angina, AMI, congestive heart failure or pulmonary edema, hypertension, hyperlipidemia, coronary artery surgery, coronary angioplasty and thrombolytic therapy. Variables concerning clinical status on admission, treatments and procedures administered, and hospital events were coded as no/not mentioned or yes. Clinical status variables included the presence of chest pain, cardiogenic shock and cardiac arrest. The delay between the onset of symptoms and paramedic/emergency department arrival was reported in minutes. Treatment for AMI, including thrombolytic therapy, cardiac catheterization, coronary angioplasty and coronary artery surgery, was noted. Finally, critical events that occurred during the course of AMI were reported; these included embolic or hemorrhagic stroke, prolonged angina, AMI extension, cardiac arrest and congestive heart failure.

Statistical methods: The chi-square statistic was used to test for differences between race and categoric variables, and the *t* test was used for continuous variables. Multiple stepwise logistic regression was used to determine whether race was associated with mortality for AMI.

TABLE I Characteristics of Patients Admitted to Coronary Care Units in Metropolitan Seattle

	White (n = 11,893)	Black (n = 641)	p Value
Age (years)	66 ± 14	58 ± 14	<0.0001
Age ≥65 years	56%	36%	0.0001
Women	42%	44%	0.18
Transporting agency			0.23
Paramedics	43%	40%	
Ambulance	18%	20%	
Self	38%	40%	
Other	1%	1%	
	(10,667)	(590)	
King County Resident	89%	95%	<0.0001
Admitted to Central City Hospital	32%	71%	<0.0001
Admission diagnosis			0.07
Rule-out myocardial infarction	74%	74%	
Unstable angina	9%	7%	
Acute myocardial infarction	5%	4%	
Other	12%	15%	
Primary discharge diagnosis			<0.0001
Acute myocardial infarction	23%	19%	
Unstable angina	22%	18%	
Congestive heart failure	7%	10%	
Dysrhythmia	8%	7%	
Cardiac arrest	1%	1%	
Hypertension	1%	9%	
Diabetes mellitus	<1%	1%	
Noncardiac chest pain	5%	2%	
Nonspecific chest pain	12%	15%	
Other diagnoses	19%	18%	
Hospital death	6%	5%	0.55

RESULTS

Chest pain population: Characteristics of patients admitted to the CCUs in the Seattle metropolitan area are listed according to race in Table I. Black persons were considerably younger ($p < 0.0001$), whereas the proportion of women in the 2 groups was similar. In addition, the mode of transportation (paramedic versus other means) to the hospital was not different in the 2 groups. However, a significantly higher percent of black persons were Seattle area residents ($p < 0.0001$); white persons were more often residents of the 2 adjacent counties (9 vs 4%). Moreover, the proportion of the black population admitted to 6 hospitals located in central Seattle was twice that of the white population. Evidence from Table I also indicates that blacks and whites differed with respect to discharge diagnosis. Hypertension was more often the primary discharge diagnosis among black patients as was congestive heart failure to a lesser extent.

Overall mortality in this diverse group of patients was 5.8%; 5.3% for black and 5.9% for white patients ($p = 0.55$). Hospital mortality for black and white men was 4.2 and 5.6% ($p = 0.26$), respectively, and did not differ when adjusted for age by the direct method of

TABLE II Characteristics of Patients with Acute Myocardial Infarction as Discharge Diagnosis

	White (n = 2,749)	Black (n = 121)	p Value
Age (years)	67 ± 13	59 ± 13	<0.0001
Women	35%	44%	0.35
Admitted to Central City Hospital	33%	69%	<0.0001
History of			
Hypertension	46%	67%	<0.0001
Hyperlipidemia	19%	19%	0.89
Acute myocardial infarction	28%	27%	0.89
Congestive heart failure	13%	10%	0.33
Angina	42%	36%	0.19
Thrombolysis	2%	3%	0.54
Cardiac catheterization	16%	12%	0.20
Coronary angioplasty	4%	2%	0.45
Coronary bypass surgery	10%	2%	0.005
Symptoms on admission			
Chest pain	90%	88%	0.50
Cardiogenic shock	4%	3%	0.97
Cardiac arrest	6%	7%	0.83
Mean time from symptom onset to hospital or emergency vehicle arrival (min)			
Mean	387 ± 929	378 ± 869	0.91
Median	106	100	

standardization. Similarly, hospital mortality for black and white women was 6.2 and 6.7% (p = 0.75), respectively, and did not differ when adjusted for age.

Acute myocardial infarction population: Baseline characteristics of the 121 black and 2,749 white patients with AMI are displayed in Table II. As in the population with chest pain, black patients were younger (p <0.0001), had more previous hypertension (p <0.0001), and were more often admitted to central city hospitals (p <0.0001). In addition, many more white patients had undergone coronary artery surgery. Black and white patients did not differ with respect to type of symptoms on admission or time from symptom onset to hospital arrival.

Diagnostic and therapeutic procedures during hospitalization for AMI are listed in Figure 2. The use of thrombolytic therapy and cardiac catheterization did not differ in the 2 groups. However, there were major racial differences in the use of angioplasty and coronary artery surgery. The number of black patients who underwent these procedures was small; 12 or 10% had angioplasty and 5 or 4% received coronary artery surgery. In comparison, 18 and 10% of white patients had angioplasty and bypass surgery, respectively; both of these rates were statistically different from those of their black counterparts. In central city hospitals, 10% of black and 15% of white patients underwent angioplasty (p = 0.20), whereas in noncentral hospitals, 11 and 20% received the procedure (p = 0.20). Furthermore, in central hospitals, 6% of black and 12% of white patients underwent coronary bypass surgery (p = 0.10), whereas 0 and 9% of black and white patients, respectively, received this procedure in noncentral hospitals (p = 0.07).

Figure 3 indicates the occurrence of various events during hospitalization for AMI. There were no differences with respect to prolonged angina, new congestive heart failure or pulmonary edema, AMI extension or cardiac arrest. Furthermore, hemorrhagic stroke as documented by computed tomographic scan was nonexistent in black patients and occurred in 0.6% of white patients (p = 0.50). The incidence of all strokes was 0.8% in the black and 2.2% in the white population (p = 0.32).

Hospital mortality was 7.4% for black and 13.1% for white patients (p = 0.07); it was 5.4% for black and 11.1% for white men (p = 0.124), and 10.6 and 16.8% (p = 0.27) for black and white women, respectively. Multivariate logistic regression analysis, using most of the variables in Table II, was used to examine if race was predictive of hospital mortality for acute AMI. After adjustment for key predictors of hospital mortality, race was not associated with hospital mortality (p = 0.38).

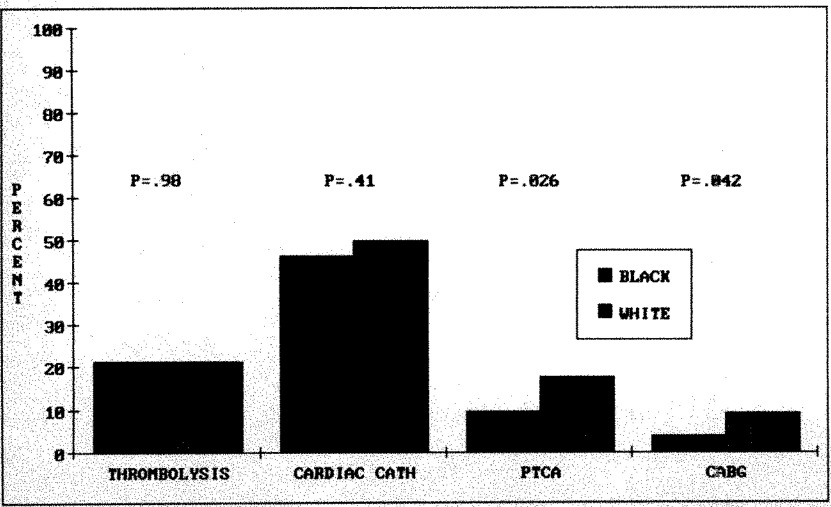

FIGURE 2. Procedures used for myocardial infarction in the Myocardial Infarction Triage and Intervention registry. CABG = coronary artery bypass grafting; CATH = catheterization; PTCA = percutaneous transluminal coronary angioplasty.

DISCUSSION

Despite differences in age, hypertension, referral patterns, and the use of certain therapeutic procedures, black and white patients with documented AMI in metropolitan Seattle had similar hospital mortality rates. Blacks with AMI were, on average, 8 years younger and had considerably more systemic hypertension than their white counterparts. The premature onset of coronary artery disease with excess hypertension has been noted in other black populations.[8] The differences in referral patterns are most likely a reflection of the residential distribution of blacks in metropolitan Seattle where they are the majority of residents in the areas served by these central city hospitals. Blacks were 4.4% of the MITI registry, and they comprised 3.5% of the metropolitan Seattle population aged >30 years in 1980.[10]

It has been reported that blacks with chest pain are less likely to seek medical attention,[1] and that they present more often without chest pain.[12] In the MITI registry, survey data were not available to determine whether black patients with chest pain were less likely to consult physicians than white patients. Furthermore in Seattle, approximately equal proportions of black and white patients with AMI presented with chest pain.

Although the use of thrombolytic therapy and cardiac catheterization was similar in the 2 groups, statistically significant differences in the use of coronary angioplasty and bypass surgery were evident in the MITI registry. Other investigators have reported that blacks were less likely to undergo cardiac catheterization and coronary artery surgery, even after controlling for severity of disease.[5,6,13,14] Because angiographic data were not available in the MITI registry, it was not possible to adjust for extent of disease. However, there is evidence that in black men and women with significant coronary artery disease, disease is severe.[4] Despite lower rates of bypass surgery, black patients have benefited from the procedure.[15-17]

In Seattle, where rates of coronary angioplasty and bypass surgery during initial hospitalization were 2.3 and 1.8 times higher in the white population, information was not available to explain these higher rates. Factors such as socioeconomic status, health insurance coverage, patient preference and extent of disease may account for the racial difference. Furthermore, hospital characteristics may be relevant, although racial differences in the use of angioplasty and bypass surgery were similar in central and noncentral hospitals. Small numbers of black patients treated at each hospital precluded analysis by individual institution. However, results from the current study and others, to a greater extent,[5,6,14] suggest a strong and consistent racial bias in the use of coronary artery surgery and other procedures in the treatment of coronary artery disease.

In metropolitan Seattle, unadjusted hospital mortality of 7.4% was lower in black patients with AMI ($p = 0.07$), but race was not predictive of hospital mortality after adjustment for key demographic and clinical variables. Investigators from Chicago's Cook County Hospital, which serves a predominantly black population, reported a 19% 2-week mortality for 111 black patients with AMI and a median time from symptom onset to hospital arrival of 6 hours, >3.5 times that for blacks in Seattle.[2] For blacks in the MITI registry with delay times >6 hours, hospital mortality was 13.6%, and although higher, was not statistically different from the 7.5% mortality associated with delay times of ≤6 hours ($p = 0.38$). Delay time was not included in the multivariate analysis, since it was unknown for 17% of both blacks and whites.

Another possible reason for lower black mortality in Seattle was that blacks with AMI had higher out-of-hospital death rates than whites[18,19] (i.e., only relatively healthy black survivors reached the hospital). Out-of-hospital deaths due to AMI were not recorded in the MITI registry, although the proportions of blacks and whites transported to the hospital with sudden death were not different.

The MITI registry has provided complete ascertainment of CCU admissions for chest pain and AMI in a defined geographic area over a 2-year period. The careful evaluation of hospital records by experienced abstracters of medical records is a further advantage of the registry. There are, however, limitations associated

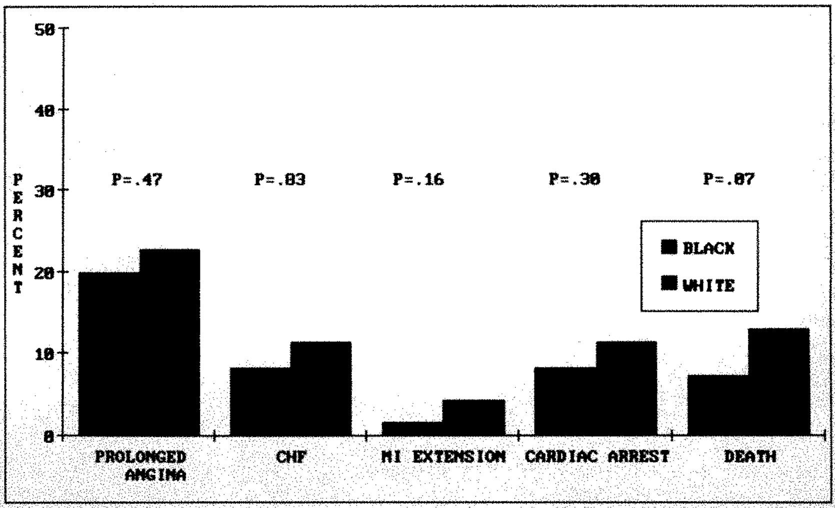

FIGURE 3. Events associated with myocardial infarction (MI) in the Myocardial Infarction Triage and Intervention registry. CHF = congestive heart failure.

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with this analysis. First, the number of blacks in the study was small; consequently, rates of death, angioplasty and bypass surgery are subject to considerable variability with the addition or deletion of just a few events. Second, these events were recorded only for the initial hospitalization for chest pain or AMI. Racial differences in the use of these 2 procedures and death rates, to a lesser extent, may be a function of the timing of these events. If these events were delayed until after hospital discharge in black patients but not in whites, then the relation between race and these events might be altered. Third, electrocardiographic information including infarct type (Q wave versus non–Q wave) and location was not available in this study, and could confound or effect the relation between race and mortality.[7] Fourth, risk factor information, including family history of coronary disease and prior cigarette smoking, was not collected.

Finally, to what degree are these findings for blacks in metropolitan Seattle relevant to other black populations in the United States? Blacks comprised <10% of residents of the city of Seattle and <5% of the metropolitan area[10]; most American cities have a much higher proportion of black residents. Moreover, the low mortality for AMI in metropolitan Seattle blacks may be a reflection of a highly responsive emergency medical system not present in all large cities. On the other hand, findings of premature coronary artery disease, excess hypertension, and the differential use of interventions have been reported.[6,8] These problems, which pervade black communities, require further attention and action on the part of government agencies and professional organizations.

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APPENDIX

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Late Results of 200 Repeat Coronary Artery Bypass Operations

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To determine the clinical outcome and the long-term results of a second coronary artery bypass operation, we studied preoperative clinical status and catheterization data in 200 consecutive patients over a 9-year period (1979 to 1987) (mean follow up time 34 months, maximum 120). The study group included 169 men and 31 women (mean age 58.4 years [7% >70 years]). Sixty-four percent of patients had severe angina (New York Heart Association class IV), 70% had 3-vessel coronary artery disease and 21% had poor left ventricular function. Reoperation was performed after a mean interval of 58 months after the first procedure. A mean of 3.3 distal anastomoses was placed. The operative mortality rate (30 days) was 7.5%, with additional cardiac morbidity (myocardial infarction, heart failure) in 11.5% of patients. Multivariate analysis showed an increased risk in women (risk ratio 3.6) and in patients with poor left ventricular function (risk ratio 3.1). The cumulative 5-year survival rate was estimated at 84%, with a rate of 77% for patients with poor left ventricular function (difference not significant). The probability of remaining free of a cardiac-related event (myocardial infarction, angioplasty, third operation, cardiac death) was 64% for 5 years. At the end of follow-up, 79% of the surviving patients were in New York Heart Association class I or II and nearly 50% of patients in the fifth year after the reoperation had good functional status. It is concluded that a reoperation is effective but carries an increased, immediate, operative risk. Late survival is good and most patients will be free of cardiac events and be in a good clinical condition in the first 5 years.

(Am J Cardiol 1991;67:24–30)

Coronary artery surgery, particularly bypass grafting, is an effective treatment for symptomatic and severe coronary artery disease. Large randomized trials, the Coronary Artery Surgery Study[1] and the European Coronary Surgery Study[2] have shown excellent results after surgery, a consistent relief of complaints and an improved survival in some subsets of patients with advanced disease. However, the progression of coronary artery disease will not be influenced by surgery and the incidence of angina pectoris 5 years after surgery is reported in up to 35% of patients.[3] If angina pectoris is not relieved by medical treatment, the patient is considered as a candidate for percutaneous transluminal coronary angioplasty or a second coronary artery bypass operation. In a large series reported from the Cleveland Clinics, the incidence of reoperations after the first procedure was 2.7% after 5 years, 11% after 10 years and 17.3% after 12 years,[4,5] up to 38% at 15 years.[6] If angioplasty is included, the reintervention rate would be even higher.[7] In the Netherlands, reoperations accounted for 6.7% of the total number of coronary bypass operations in the year 1988.[8] A reoperation necessitates specific modifications in technique and is regarded as more difficult and having an increased risk. We studied the clinical outcome and long-term follow-up in a group of 200 patients who underwent a reoperation between 1979 and 1987.

METHODS

Patient population: During the period from November 1979 to April 1987, 200 consecutive patients who underwent reoperation were included in our study group. Patients who had a combined procedure, e.g., valve replacement or aneurysmectomy and patients who underwent a third operation were excluded.

CLINICAL AND CATHETERIZATION DATA: All clinical documentation, correspondence and catheterization information were reviewed by protocol and processed in a structured database. Clinical data included clinical history, severity of angina pectoris, surgical information of both operations and follow-up. Angina pectoris was classified according to criteria of the New York Heart Association. Death within 30 days after reoperation was considered as operative mortality and after 30 days as late mortality. Complications within 30 days were recorded in patients who died within that period, with the exclusion of those complications. Morbidity after hospital discharge was registered only when it resulted in a hospital admission, mainly for a myocardial infarction, a third bypass operation or an angioplasty. The coro-

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nary arteriograms before the first (89%) and before the second (96.5%) operation, together with the hemodynamic measurements and the left ventriculograms, were reviewed. The angiographic indication for reoperation could be determined in 93%. If original recordings were missing, final classification was determined with information from clinical documentation. Luminal narrowing >50% (biplane) was classified as a significant stenosis and >90% stenosis as a subtotal occlusion. Grading of coronary artery disease was based on the sum of significant stenoses in proximal major coronary arteries; a significant stenosis in the main stem of the left coronary artery was regarded as equivalent to 2-vessel disease, but was also entered in the final analysis as an independent determinant. Progression of coronary artery disease was defined as a new significant stenosis or the transition of a preexistent significant stenosis to a subtotal or total occlusion. A significant stenosis, a subtotal or total occlusion in a bypass graft was registered as graft failure.

Left ventricular function was categorized using left ventricular end-diastolic pressure combined with analysis of left ventricular regional wall motion at ventriculography (biplane 7 segments, single plane only 5 segments). Left ventricular function was classified as impaired if 1 to 2 segments showed hypokinesia or akinesia, or if the end-diastolic pressure was >20 mm Hg. Left ventricular function was considered poor where 1 or 2 segments were abnormal and left ventricular end-diastolic pressure was >20 mm Hg, or if >2 segments showed abnormal wall motion.

SURGICAL TECHNIQUE: Reoperation was performed through a median sternotomy with an oscillating saw and deflated lungs. Adhesions of the retrosternal space and the mediastinum were dissected sharply or with the coagulator. The ascending aorta and the right atrium were cannulated with standard techniques. The coronary arteries were identified before cross-clamping of the aorta, and this identification was often difficult because of very small vessels or extensive coverage with adhesions. The major saphenous vein was used for grafting with, as an alternative, the saphenous parva vein, usually from the left leg. More recently, we started using the left internal mammary artery. After cross-clamping the aorta, myocardial preservation was achieved by anterograde perfusion of the St. Thomas Hospital solution in the coronary arteries, combined with topical cooling. After the distal anastomoses were placed, the proximal anastomoses were constructed often using the previous vein grafts on the aorta.

FOLLOW-UP DATA: Data on clinical course after reoperation and clinical status at the end of follow-up were collected from the outpatient clinical records of the attending cardiologists. If this approach was not possible, a questionnaire was answered by the attending cardiologist. An identical questionnaire was presented to all general practitioners. We received information from 94% of the general practitioners and from 98% of the cardiologists. A definite judgment of clinical status at the end of follow-up was based on the least favorable score. Late mortality was confirmed by the registry office. The end of the follow-up period was January 1, 1988. Follow-up data were available for 99% of the patients; 10% of the patients died during the study period and 1% of patients was lost to follow-up. The total follow-up time was 635 patient-years; the mean follow-up time of patients was 34.4 months (maximum 120).

STATISTICAL ANALYSIS: Differences between proportional variables were tested with a chi-square test and, in the case of a small number set, the Fischer exact test was used. Differences between continuous variables were tested with Student's *t* test. A logistic regression procedure was applied for multivariate analysis of the surgical mortality. The Cox proportional-hazards model was used for multivariate analysis of survival and the event-free period. The covariates (potential risk factors or determinants) were dichotomized and entered in the analysis as indicator variables for which the value of 0 or 1 was assigned: gender (men = 0, woman = 1); age (<70 years = 0, >70 years = 1); interval between the first and second operation (<12 months = 0, >12 months = 1), angina pectoris (class II and III = 0, class IV = 1); coronary artery disease (1- and 2-vessel disease = 0, 3-vessel disease = 1); left main disease (stenoses <50% = 0, >50% = 1); and number of distal anastomoses placed at second operation (<3 = 0, >3 = 1). Left ventricular function was entered in the model as normal, impaired and poor. Cumulative survival and event-free periods were estimated by the Kaplan-Meier method. A significance level of $p = 0.05$ was used in all tests. The multivariate analysis was performed with the B.M.D.P. package.

RESULTS

Two hundred patients underwent reoperation; 87% were men. The ages ranged from 36 to 78 years (mean ± standard deviation 58.4 ± 8.2) including 14 patients >70 years. Women were, on average, 5 years older than men. At the first operation, of which 68% were performed in our center, a mean of 2.7 distal anastomoses were placed. The mean interval between the first and the second operation was 58 months (standard deviation 40, range 2 to 169). At some time before reoperation, 68% of the patients had had a myocardial infarction.

Clinical indication for reoperation was severe angina pectoris class III (34%) or IV (64%) despite drug treatment. Coronary arteriography showed 1-vessel disease in 5%, 2-vessel disease in 24.5% and 3-vessel disease in 70.5% of patients. Left main coronary artery disease was present in 14.5% of patients. Left ventricular function was normal in 48%, impaired in 30.5% and poor in 21.5% of patients. In 28.5% of the patients, graft failure was the cause of return of angina pectoris, in 20% progression of coronary artery disease and in 42% a combination of these causes existed.

Incomplete revascularization at the first operation was presumed in 14.5% of the patients and was the only indication for reoperation in 2.5%. Figure 1 shows the association of the interval between operations and the angiographic indication. In Table I the comparison is made between the first 40 and the last 40 patients of our study group indicating that the patients' character-

TABLE I Comparison of the First 40 and the Last 40 Patients

	First Group	Last Group	p Value
Mean age (years)	55.3	60.2	<0.01
Interval from first to second operation (mos)	36	61	<0.01
Distal anastomoses (first operation)	2.2	2.8	<0.1
Graft failure (%)	42.5	30	>0.1
Progression of CAD (%)	53	61	>0.1
3-vessel disease (%)	63	78	>0.1
Impaired and poor LV function (%)	48	60	>0.1
Distal anastomoses (second operation)	2.7	3.6	<0.01

CAD = coronary artery disease; LV = left ventricular.

TABLE II Surgical Data, Operative Mortality and Complications

Elective procedures (%)	69
Grafts	1.8
Internal mammary artery graft (%)	6.5
Distal anastomoses	3.3
Clamp time (min)	54
Bypass time (min)	87
Operative mortality (%)	7.5
Mortality within 24 hours (%)	5.5
Cardiac mortality (%)	6.5
Nonfatal cardiac complications (%)	11.5
Myocardial infarction (%)	4.0
Heart failure (%)	10.0
Rethoracotomy (%)	5.5
Infection (%)	5.0
Mediastinitis (%)	2.0

istics have changed during the study period. More elderly patients, with a longer interval between the first and the second operation, and with a longer duration of illness and a more extensive revascularization at the first operation are currently undergoing operation for a second time. Although not significant, a shift to more extensive coronary artery disease with poorer left ventricular function was noticed.

Operation: All operations were performed according to the previously described method. In 3 patients, no cardioplegia was used: in 1 because the operation was limited to a partial resection and reconstruction of an occluded vein graft and in 2 because only intermittent cross-clamping was used. A mean of 3.3 distal anastomoses was placed for which a mean of 1.8 grafts was used.

The *operative mortality* was 7.5%; most patients died within the first 24 hours (5.5%). The main cause was myocardial infarction (5.0%) followed by heart failure (1.5%). A logistic regression analysis marks left ventricular function and gender as independent determinants of operative mortality. The relative risk of a patient with poor left ventricular function compared with a patient with normal left ventricular function is 3.1 (95% confidence interval 1.1 to 8.9). Female patients have a relative risk of 3.6 (95% confidence interval 1.4 to 9.0) compared with male patients.

Operative morbidity (nonfatal complications): Cardiac complications occurred in 11.5% of patients, myocardial infarction in 4.0% and severe heart failure in 10% (2.5% secondary to a myocardial infarction). In 5% of patients an infection was treated and 2% had a mediastinitis. Rethoracotomy was performed in 5.5% of the patients. Table II summarizes surgical data, operative mortality and morbidity.

Late mortality and survival: Cardiac mortality after hospital discharge occurred in 7.6% of the patients and 2.7% died of another cause. The cumulative 5-year survival rate after hospital discharge was estimated at 84%. Patients with poor left ventricular function tend to have a less favorable prognosis with a 5-year survival of 77% (versus those with normal left ventricular function 89%, p = 0.5). The multivariate model indicated only angina pectoris, the interval between the operations and the number of distal anastomoses as independent determinants of survival. The cumulative 5-year survival rate of patients with angina pectoris class IV was 80% (vs 91%, p = 0.08), of patients with an interval of <12 months 78% (vs 100%, p = 0.07), and of patients with <3 distal anastomoses 81% (vs 90%, p = 0.09). Figure 2 shows the cumulative survival rate of patients with normal and poor left ventricular function.

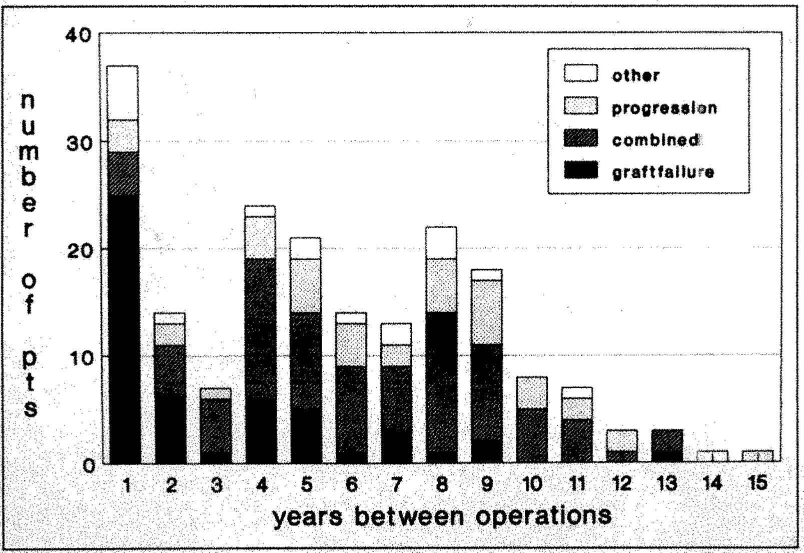

FIGURE 1. Distribution of the patients according to the interval between the first and second operation and the angiographic indication for surgery.

Late morbidity: After hospital discharge, 11.9% of the patients had a myocardial infarction, 3.3% underwent a third coronary artery bypass operation and 4.9% a coronary angioplasty. One or more new interventions were performed in 7.6% of patients. The probability of remaining free of a cardiac-related event (myocardial infarction, a third intervention or a cardiac death) during a 5-year period was 64% for the total study population, but was 42% for patients with poor left ventricular function (versus normal left ventricular function, 73%; $p = 0.11$) and 53% for patients with angina pectoris class IV (versus angina pectoris class II to III, 87%; $p = 0.005$). The Cox multivariate model indicated only angina pectoris as an independent determinant. Figure 3 shows the influence of left ventricular function on the clinical course. Figure 4 shows the functional class of patients without any cardiac-related event, together with the cardiac-related events or noncardiac death of the remaining patients, presented in years since the reoperation. In the fifth year after reoperation, >50% of patients have severe angina pectoris or had had a cardiac event.

Clinical status at the end of follow-up: According to general practitioners, cardiologists and the least favorable score, severe angina pectoris class III or IV was present in 10, 19 and 21% of patients. In 24% of the patients, the general practitioner and the cardiologist agreed on a clinical status free of angina pectoris. Success, no angina or angina pectoris class II were assessed in 79% of the patients. Figure 5 shows the clinical status at the end of the follow-up, presented by years since the reoperation. Table III summarizes the clinical course after hospital discharge and Table IV shows clinical status at the end of follow-up.

DISCUSSION

The number of reoperations for coronary artery disease is increasing. Reoperations will become the second most common procedure in the field of cardiac surgery and will cover ≥10% of all coronary bypass operations in the near future. If all symptomatic patients after a coronary bypass operation were considered as potential candidates for reintervention, the present situation would resemble an "iceberg" phenomenon. Because of the early onset of large-scale coronary bypass surgery, centers in the United States have provided most of the information on the subject of reoperations. The results of American studies may not be applicable to the Euro-

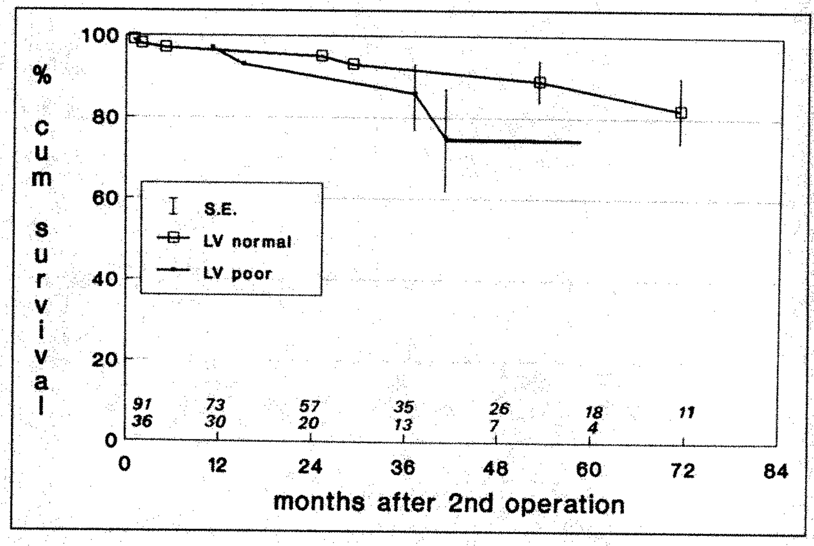

FIGURE 2. Late survival of 185 patients after hospital discharge according to left ventricular (LV) function graded normal, subnormal (not shown) and poor. cum = cumulative; S.E. = standard error.

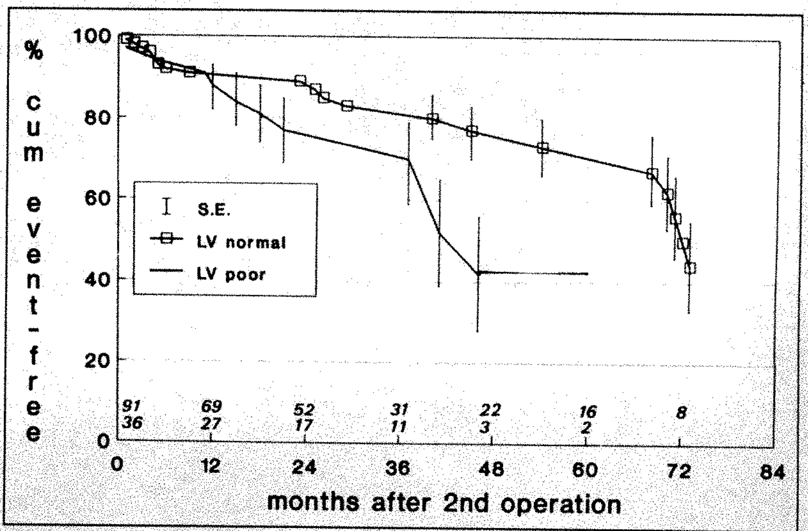

FIGURE 3. Cardiac-related event-free period of 185 patients after hospital discharge according to left ventricular (LV) function graded normal, subnormal (not shown) and poor. Abbreviations as in Figure 2.

TABLE III Clinical Course After Hospital Discharge

Number of patients	185 (100%)
No follow-up (%)	0.5
Late mortality	
Cardiac cause (%)	7.6
Noncardiac cause (%)	2.2
First-year mortality (%)	2.7
5-year survival (%)	84
Late cardiac morbidity	
Myocardial infarction (%)	11.9
Angioplasty or third operation (%)	7.6
5-year cardiac-related event free (%)	64

Cardiac event = myocardial infarction, angioplasty, third operation or cardiac death.

TABLE IV Clinical Status at the End of Follow-Up

Number of patients	165 (100%)
Lost to follow-up	1
No complaints	57 (35%)
Angina pectoris NYHA class II	73 (44.5%)
Angina pectoris NYHA class III/IV	34 (21%)

NYHA = New York Heart Association.

pean setting. The more restrictive approach of many European countries to cardiac surgery leads to a different patient group undergoing reoperation, with more severe angina pectoris.[9,10]

The objective of our study was to determine the clinical outcome and long-term results of reoperations in our center. We found an operative mortality of 7.5% and a 5-year cumulative survival after hospital discharge of 84%. Comparative studies have reported that the operative mortality of reoperation is higher than that of a first operation.

Pooled data of the State of New York registry showed an operative mortality of 11.7% in 1987.[11] The results of different centers are presented in Table V. Importantly, Table V also shows some significant differences in patient selection resulting in an important shift in baseline characteristics. There is a large range of the mean age, the interval between the first and the second operation, the severity of angina pectoris and the degree of ventricular dysfunction. Some investigators include

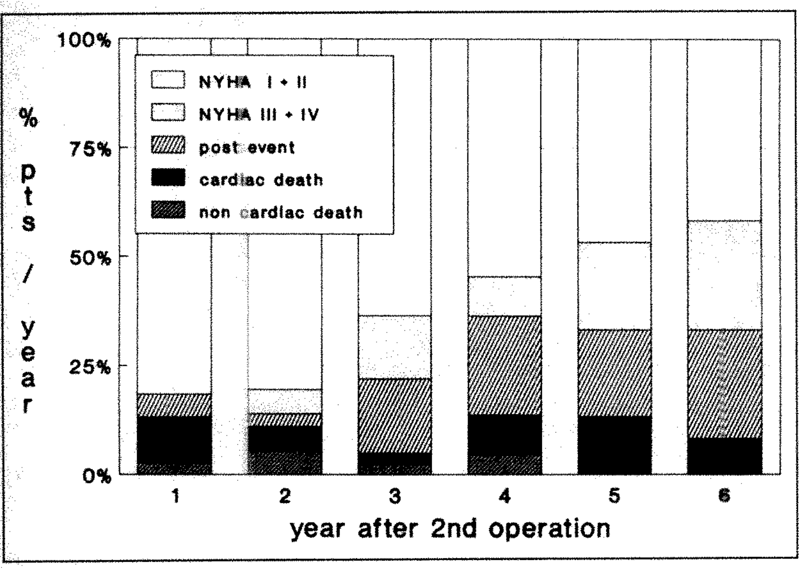

FIGURE 4. Histogram of 185 hospital survivors according to their clinical course after discharge and presented by years of follow-up time since reoperation. Only patients without any event (myocardial infarct or third intervention) were classified according to New York Heart Association (NYHA) class I or II or class III or IV. The remaining patients were categorized as "post event" if, during follow-up, any cardiac-related event had occurred. The deaths were registered at the actual time.

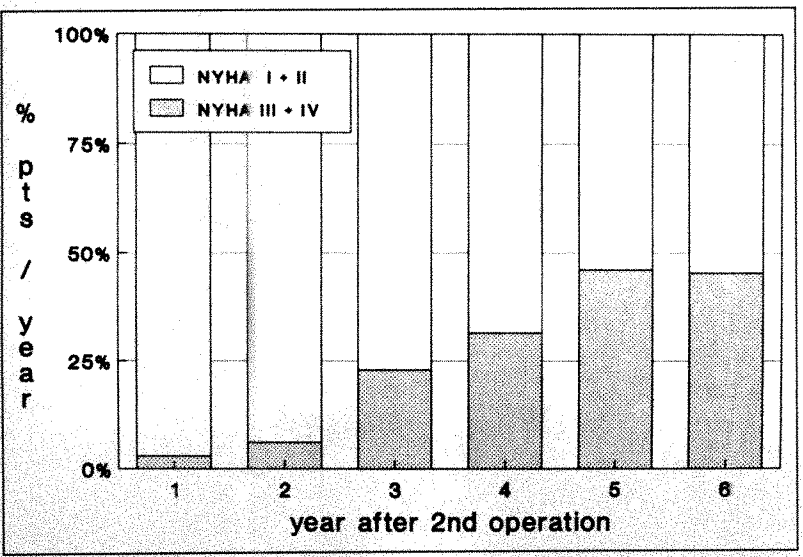

FIGURE 5. Histogram of 165 patients alive at the end of follow-up, according to their clinical status at the end of the follow-up time, and presented by years of follow-up time since reoperation. Patients were classified according to New York Heart Association (NYHA) class I or II or class III or IV.

TABLE V Comparison of Results from Published Reports

Center	No. of Pts.	Mean Age (yrs)	Interval Operations (mos.)	Angina Class IV	LV Dysfunction (%)	Operative Mortality (%)	Survival (yrs) (%)
Cleveland 1982–84	625	58	84	25	66	3.4	90 (5)*
Clinics[5] 1979–81	439	56	72	30	60	2.3	75 (10)*
1967–78	436	53	50	28	40	4.6	
Thoraxcentrum Dijkzigt[6]	99	—	—	—	—	6.6	
Harvard[12]	112	50	36	—	—	4.0	94 (3.8)†
London Chest Hospital[13]	102	52.7	37	—	—	2.0	
CASS registry[14]	283	52	39	—	—	5.3	
Mayo Clinics[15]	106	49	—	37	—	2.8	94 (5)
Texas Heart Institute[16]	168	51.4	—	84	53	4.8	82 (6)†
A.M.C.	200	58.4	58.3	64.5	52	7.5	84 (5)

* All periods together.
† Nonactuarial estimate of survival.
LV = left ventricular.

combined procedures, e.g., aortic valve replacement or a third bypass operation. In the present study we noticed, like others, a trend toward reoperation of older patients with a longer duration of illness and more advanced coronary artery disease. Both the increasing efficacy of coronary angioplasty as an alternative for bypass surgery and the use of the internal mammary artery as a graft at first operation has delayed reoperation, resulting in an increase in the number of reoperations in later stages of the disease.[4,17] More distal anastomoses are placed on coronary artery branches with small lumina, whereas a number of lesions do not offer any possibility for bypass graft surgery. The prolonged time on extracorporeal circulation, a more difficult myocardial protection and the increased risk of postoperative hemorrhages, all increase the operative mortality.

In our study, the 5-year survival was 84% and the probability of an event-free period of 5 years was 64%. In general, survival after reoperation is favorable and is reported as ranging from 84 to 90% for the first 5 years. In addition, some studies compared survival after a first and second operation and found no major differences.[5,6] In our study, multivariate analysis indicated left ventricular function as an independent determinant for operative mortality but not for long-term survival. This is in contrast to the Cleveland series and some other reports and could be explained by the transition of mortality to the first 30 days, resulting in selection of survivors.[5] The higher risk of women for operative mortality is reported by others, but could be biased by factors not monitored for in the analysis as recently shown by Kahn.[18] Other multivariate independent determinants of long-term survival were not significant in the univariate analysis and the interpretation needs a larger patient group or longer observation time. The benefits of reoperation are, to a great extent, determined by quality of life, expressed by the functional class.

Clinical status at the end of follow-up was good in 79% of the patients and 35% had no complaints. Functional class decreased as time elapsed after reoperation. At 5 years after operation almost half of the patients had severe angina pectoris again. Our findings are consistent with other studies that also reported a high recurrence of angina pectoris.[12] The evaluation of the clinical status at the end of follow-up is determined by the study design. If we change the method of assessment of clinical status from the least favorable score of one of the questionnaires to the best score of general practitioner or cardiologist, we would have found a success rate of 88.6, and 56% of patients would have been free of complaints. Differences in judgment of clinical status are explained in 2 ways: First, general practitioners sometimes include noncardiac complaints in their final score; and second, the general practitioner has not seen the patient for a long time and provides an indirect reference. As a result, the cardiologist has a 92% agreement with the definitive rating in contrast to the general practitioner with a 60% agreement. The discrepancies between the rating of functional class emphasizes the subjective nature of the published results.

Study limitations: No effort was made to stratify the patients according to risk factors for atherosclerosis and prevention of graft thrombosis after reoperation in our study because of its retrospective nature. The extent of coronary artery disease was assessed by means of the sum of proximal stenoses in major coronary arteries and does not account for the more diffuse atherosclerotic disease and peripheral lesions, although this might have an influence on the outcome. The degree of left ventricular function was based on a score of the wall motion combined with the presence of a high left ventricular end-diastolic pressure. The use of the ejection fraction was rejected because it requires ventriculograms, sometimes lost for review or not repeated before the reoperation. Although the value of left ventricular function is qualitative, the distinction between normal and poor is clear and provides a contrast in the multivariate analysis. Neither serial arteriography to assess graft patency, nor an objective measurement of functional status, particularly exercise testing, was performed.

Conclusion: Our results demonstrate that a reoperation is effective, but carries an increased operative mortality, especially in patients with poor left ventricular function and in women. Late survival is good and most patients will be free of cardiac events and be in a good clinical condition for the first 5 years. The question of whether reoperation is preferred over medical treatment needs to be answered by a randomized trial, but this will probably never be conducted. In his comments on major trials in the field of coronary bypass surgery, Killip[19] points out the relation between increased risk of operative mortality and prolonged survival after surgery compared with medical treatment. If such a relation exists in the domain of reoperations, then prolonged survival warrants the performance of these procedures despite the increased risk, and for patients with severe angina pectoris it will offer not only years to life but also life to years.

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Cardiovascular Risk Factor Clustering and Ratio of Total Cholesterol to High-Density Lipoprotein Cholesterol in Angiographically Documented Coronary Artery Disease

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High levels of cardiac risk factors tend to cluster together and act synergistically. To develop a suitable and practical marker for clustering, we evaluated 380 consecutive patients at the time of coronary angiography. Analyses of lipid, rheologic, clinical and arteriographic profiles indicated a variety of interwoven relations. Because the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol (total/HDL cholesterol) was closely related to both the presence and extent of $\geq 50\%$ diameter reduction of ≥ 1 coronary arteries, it was used to divide patients into quartiles. Clustering of high- and low-level risk factors was demonstrated in the highest and lowest quartiles of total/HDL cholesterol, respectively ($p < 0.001$). The highest quartile may be characterized by an only moderately elevated total cholesterol level but patients in this quartile may have a very low HDL cholesterol level, high triglycerides, a tendency toward high hemoglobin and fibrinogen levels, a history of smoking, previous myocardial infarction and multivessel disease. These results suggest that total/HDL cholesterol serves as a marker not only for obstructive coronary disease but also for a cluster of potentially modifiable risk factors.

(Am J Cardiol 1991;67:31–36)

Coronary artery disease has been related to a number of factors, including blood lipids,[1-3] hemoglobin and hematocrit,[4,5] fibrinogen,[6-9] smoking,[10] and diabetes.[11] There is also mounting evidence that many of these risk factors cluster together and act synergistically especially when present at their higher levels.[12,13] To characterize our cardiologic population and, with the aid of risk factor clustering, develop a clinical, multivariate approach toward eventual secondary prevention, we evaluate a group of risk factors routinely obtained in patients undergoing diagnostic coronary arteriography at a large referral medical center, and demonstrate that clustering of high-level risk factors may be readily identified by a marker: the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol (total/HDL cholesterol).

METHODS

Patients were studied between January and October 1989. Within a week before coronary angiography, an outpatient examination was performed, fasting blood sample drawn and a resting electrocardiogram recorded. Results of history and physical examination were tabulated by the examining cardiologist with the standardized computer program of the Hadassah University Hospital Department of Cardiology. The presence of systemic hypertension was determined by diagnostic history and blood pressure measurement $>160/90$ mm Hg or by the use of antihypertensive medications. Diabetes was considered present if there was a diagnostic history confirmed by a fasting blood sugar >140 mg/dl or antidiabetic treatment. Smoking was considered a factor if the patient had either smoked or stopped smoking during the last 5 years >10 cigarettes per day for ≥ 5 years. Cholesterol,[14] HDL cholesterol[15] and triglyceride[16] levels were determined in duplicate by enzymatic methods in the Hadassah Hospital laboratories of Drs. E. Stein and O. Stein, where lipids are standardized with the Lipid Research Clinics Program. Fibrinogen values were determined in the Hadassah Hospital laboratory of Dr. A. Eldor with an automated coagulation laboratory analyzer using calcium thromboplastin.[17] In our data, fibrinogen values were found to be related to age; age-adjusted values are therefore reported. Viscosity was calculated from hematocrit and total protein using the formulas of Simone et al.[18] Because we found that the viscosity relations evaluated in the

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TABLE I Mean Values and Prevalence of Continuous and Discrete Variables in Men and Women

	Total	Men	Women
Continuous Variables (Mean ± SD)			
No. of pts.	380	300	80
Age (yr)	58 ± 11	57 ± 10	59 ± 13
Total cholesterol (mg/dl)	224 ± 43	222 ± 43	232 ± 42
HDL cholesterol (mg/dl)	40 ± 10	39 ± 10*	45 ± 11
Total/HDL cholesterol	5.9 ± 1.6	6.0 ± 1.7*	5.3 ± 1.2
Triglycerides (mg/dl)	154 ± 76	158 ± 80**	138 ± 58
Fibrinogen (mg/dl)§	338 ± 92	335 ± 93	343 ± 91
Hemoglobin (g/dl)	14.7 ± 1.4	15.0 ± 1.3*	13.7 ± 1.5
Hematocrit (%)	46 ± 5	46 ± 4*	43 ± 5
Total protein (g/dl)	7.1 ± 0.5	7.1 ± 0.5	7.0 ± 0.5
Viscosity (centipoises)	4.6 ± 0.6	4.7 ± 0.5*	4.2 ± 0.6

	No. of Pts.	Prevalence (%)	Men	Women
Discrete Variables				
Cigarette smoking	167	44	155†	12
Diabetes mellitus	61	16	52	9
Systemic hypertension	127	33	108‡	19
Previous myocardial infarction	128	34	113‡	15
Coronary artery† ≥50% reduction in diameter	95	25	57	38
1	89	23	72	17
2	86	22	78	8
3	110	28	94	16

For men and women, * p <0.001; ** p <0.02; † p <0.001 by chi-square analysis; ‡ p <0.05 by chi-square analysis; § 180 patients (age-adjusted): 137 men, 43 women.

HDL = high-density lipoprotein; SD = standard deviation; total/HDL cholesterol = ratio of total cholesterol to high-density lipoprotein cholesterol.

present study exhibited no differences among any of the various specific shear rates reported by Simone et al, we report only viscosity in centipoises at a shear rate of 208 s^{-1}, which is comparable to the shear rate in the coronary artery. Coronary angiograms were obtained with the Judkins percutaneous retrograde femoral artery technique, using a high resolution 4.5-inch General Electric image intensifier, and were filmed at 25 frames/s. All films were reviewed by ≥2 observers without specific knowledge of blood laboratory results. Significant occlusive disease was defined as ≥50% diameter obstruction of a major coronary vessel. Extent of disease was defined as the number of major coronary arteries with significant occlusive disease. These arteries comprise the left anterior descending coronary artery with its major diagonal branch, the right coronary artery and the circumflex coronary artery with its major marginal branch. Depending on dominance, the posterior descending coronary artery was included as part of the right coronary artery or circumflex coronary artery. In case of disagreement among observers in this independent visual estimation, a final result was reached by mutual consensus.

Statistical analysis: Statistical analysis was performed with standard methods for 2-tailed unpaired Student's *t* test, chi-square analysis and correlation coefficients. For comparison of multiple groups of continuous variables, we used analysis of variance with Duncan's multiple-range test for comparisons. We also used multivariate regression analysis with an SPSS-11 program on a PDP-11/34 computer and with an SPSSX program on a Microvax 3900 computer. Because total/HDL cholesterol with both univariate and multivariate analyses was closely related to the presence and extent of coronary artery disease, and was clinically suitable as opposed to a more invasive evaluation such as coronary angiography, we selected the ratio to be used as a marker for other risk factors. We used the range of both the highest and lowest quartile of individual continuous variables to determine high and low levels of these variables, except for HDL cholesterol, in which the opposite was determined. Discrete variables were considered as if they were in the highest quartile by their very presence and in the lowest quartile by their absence. Similarly, the finding of 3-vessel disease was assigned to the highest quartile and that of no significant vessel disease to the lowest quartile.

Patient population: Patients whose laboratory values or coronary anatomy might be altered by a clinical event or by pharmacologic or mechanical intervention were excluded. These included those who had had a recent acute myocardial infarction, prior percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, had received streptokinase, were accepted for angiography on an emergency basis, had a hematocrit level below 35% or were receiving antilipemic agents, thyroid preparations or estrogens. From a total of 666 consecutive patients undergoing coronary arteriography during the period of this study, 380 patients did not have any of these excluding factors and were included. Sixteen of these patients had been receiving coumarin-type anticoagulant drugs, 51 were taking diuretics and 126 were on a regimen that included β-adrenergic blocking agents. Total cholesterol, HDL cholesterol and total/HDL cholesterol values were not significantly different when comparing patients receiving or not receiving β-adrenergic blocking drugs. Triglycerides, however, were significantly higher in patients taking these agents (172 ± 92 vs 145 ± 65 mg/dl [$p < 0.01$]). Information on each of the continuous and discrete variables was obtained in almost every patient; however, due to a delay in instituting fibrinogen testing, fibrinogen level was determined in only 180 patients.

RESULTS

Values (mean ± standard deviation) for continuous variables and prevalence of discrete variables are listed in Table I. Most subjects were men who, in comparison with women, had significantly different lipid and rheologic values and a greater prevalence of discrete variables.

Continuous variables: Univariate analysis for continuous variables generally showed highly significant statistical differences ($p < 0.01$) between no significant disease and the presence of either 1-, 2- or 3-vessel disease. P values for many correlation coefficients relating 1 continuous variable to another were often in a significant range; however, in most cases, the correlation coefficients were below 0.200. Triglycerides were exceptional, in that r values relating triglycerides to total choles-

TABLE II Significant Relations Between Continuous Variables and Discrete Clinical-Risk Factors (*t* Test)

Smoking	p Value	Diabetes	p Value	Hypertension	p Value	Previous MI	p Value
Triglycerides	<0.01	Fibrinogen	<0.05	HDL cholesterol	<0.05	HDL cholesterol	<0.02
Hemoglobin	<0.001			Hemoglobin	<0.002	Hemoglobin	<0.01
Hematocrit	<0.001			Hematocrit	<0.001	Hematocrit	<0.002
Viscosity	<0.001			Viscosity	<0.001	Viscosity	<0.001
Total/HDL cholesterol	<0.05					Total/HDL cholesterol	<0.01

The mean level of a continuous laboratory variable in patients with the discrete clinical factors of smoking, diabetes, hypertension or previous myocardial infarction is related to the mean level in patients without the presence of the listed discrete variable. Except for high-density lipoprotein cholesterol, the mean was always higher in the group with the presence of the risk factor. Only those variables with significant differences ($p < 0.05$) are included.

MI = myocardial infarction; other abbreviations as in Table I.

TABLE III Continuous Variables and Extent of Obstructive Coronary Artery Disease

					Significance of F Coefficient	Significant Pairs
	Analysis of Variance in 380 Patients					
No. of coronary arteries ≥50% reduction in diameter	0	1	2	3		
No. of pts./age (yr)	95/54	89/56	86/58	110/62	0.001	0–3, 1–3
Total cholesterol (mg/dl)	213	226	227	230	0.025	0–3
HDL cholesterol (mg/dl)	43	41	39	39	0.017	0–3
Total/HDL cholesterol	5.2	5.8	6.1	6.3	0.0001	0–1, 0–2, 0–3
Triglycerides (mg/dl)	135	159	159	160	0.059	—
Fibrinogen* (mg/dl)	324	343	335	352	0.473	—
Hemoglobin (g/dl)	14.3	15.2	14.7	14.8	0.001	0–1
Hematocrit (%)	44	47	46	46	0.001	0–1
Total protein (g/dl)	7.0	7.1	7.3	7.1	0.537	—
Viscosity (centipoises)	4.4	4.8	4.6	4.6	0.766	—

* 180 patients (age-adjusted).

Significant pairs = pairs of vessel disease groups that are significantly different as calculated by Duncan's multiple-range test for comparisons; other abbreviations as in Table I.

terol, HDL cholesterol and total/HDL cholesterol were 0.388, 0.389 and 0.653, respectively (all $p < 0.00001$). The correlation coefficient for age and fibrinogen levels was 0.289 ($p < 0.001$).

Discrete variables: A variety of interrelations were demonstrated when discrete clinical variables were correlated with one another: hypertension was related to previous myocardial infarction ($p < 0.01$), smoking ($p < 0.001$) and diabetes ($p < 0.05$), whereas smoking was related to diabetes ($p < 0.01$) and previous myocardial infarction ($p < 0.01$). Blood rheologic factors were significantly related to smoking, diabetes, hypertension and previous myocardial infarction when discrete clinical variables were related to laboratory values (Table II).

Vessel disease: Analysis of variance, relating extent of coronary disease to continuous variables (Table III), provided a variety of significant correlations. Chi-square analysis of discrete variables indicated a relation only for previous myocardial infarction to extent of disease ($p < 0.01$). When we used multivariate stepwise regression analysis for all factors analyzed, the significant factors related to extent of disease were total/HDL cholesterol, age, diabetes and gender.

Ratio of total cholesterol to high-density lipoprotein cholesterol: We then sought to clarify the multitude of relations among both continuous and discrete variables. Because the ratio was closely related to both the presence and extent of coronary artery obstructive disease as well as to a variety of other factors, and was clinically suitable as a marker, we divided our patients into quartiles of 95 patients each by ratios of 0 to 4.67, 4.68 to 5.63, 5.64 to 6.72 and 6.73 to 15.00. It is notable that from quartile 1 to 4 the percent decrease in HDL cholesterol levels was greater (38%) than the increase in total cholesterol levels (24.5%). Many patients with high ratios may not necessarily have an elevated level of total cholesterol; the high ratio thus indicating a reduced level of HDL cholesterol. Because of these differences, we included total cholesterol and HDL cholesterol as separate variables in the analyses.

Factors emerging from an analysis of variance indicating that the mean values for the quartiles were not all equal are shown in Figure 1. Age-adjusted fibrinogen values are included, although the significance of the F coefficient was >0.05, at 0.076. Duncan's multiple-range test for comparisons did not demonstrate statistically significant differences between any 2 quartiles of hemoglobin or fibrinogen values; statistically significant differences were present, however, among most quartiles for the other continuous variables. Chi-square analysis of discrete variables indicated statistical significance for smoking, previous myocardial infarction and extent of vessel disease. The top quartile of patients according to total/HDL cholesterol may be characterized as those patients with an only moderately elevated cholesterol level, but an extremely low HDL cholesterol level, high triglycerides, a tendency toward high hemoglobin and fibrinogen levels, a history of smoking, previous myocardial infarction and multivessel disease.

The determination of high and low levels of those variables to be used for clustering is described in the Methods section. A greater percentage of patients in quartile 4 have ≥4 risk factors at their higher levels than do patients in quartile 1 ($p < 0.001$) (Figure 2, top). However, if quartile 1 is evaluated when risk factors are no longer taken at their most abnormal levels, a shift in the distribution of patients with multiple risk factors occurs; a greater percentage of patients have multiple risk factors in quartile 1 ($p < 0.001$), but only if the risk factors are at their low levels (Figure 2, bottom). If total cholesterol and HDL cholesterol are excluded from the cluster analyses, the significance of association between ratio quartiles and the number of both high- and low-level risk factors remains ($p < 0.001$). Because of the differences in risk factors between men and women, we also performed separate cluster analyses on men and women. For men, the cluster analyses for both high- and low-level risk factors continued to be very significant ($p < 0.001$). For the smaller group of women, clustering of high-level but not of low-level risk factors was seen ($p < 0.001$). Because triglyceride levels were closely related to total/HDL cholesterol and were also significantly higher in patients receiving β-adrenergic blocking agents, we performed cluster analyses on the 254 patients who were not receiving β blockers: The total/HDL cholesterol quartile analysis for clustering was very similar for high-level ($p < 0.001$) and also for low-level risk factors ($p < 0.001$).

DISCUSSION

Interwoven relations: A variety of mechanisms that involve lipid,[19] rheologic,[20] metabolic and endocrinologic factors[21] may be related to the presence of occlusive coronary artery disease. The present study demonstrates that these factors are often interwoven through an intri-

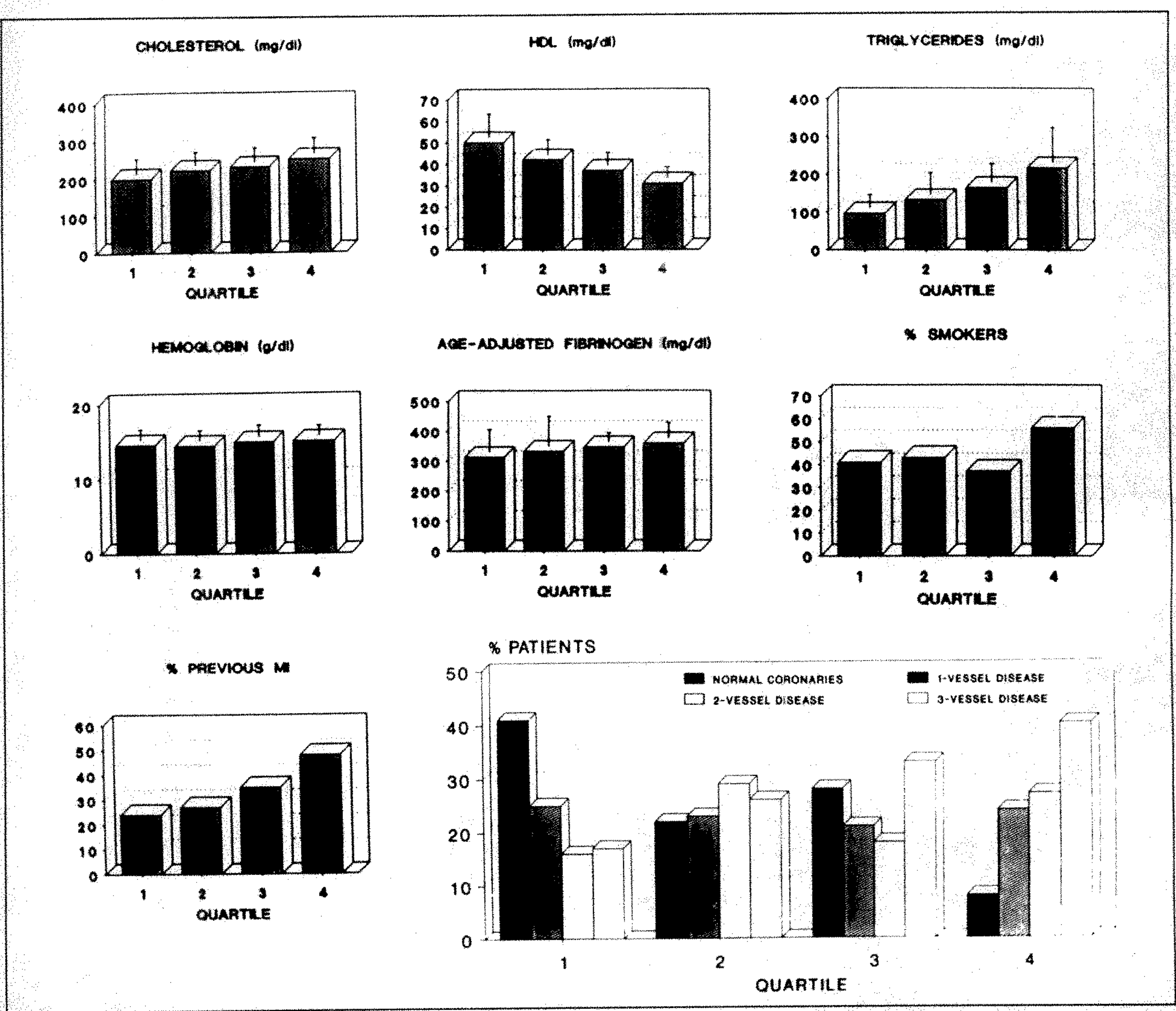

FIGURE 1. Relation of risk factors to quartiles of the ratio of total cholesterol (cholesterol) to high-density lipoprotein (HDL) cholesterol (mean ± standard deviation). Analysis of variance statistical probabilities are <0.001 for total cholesterol, <0.001 for HDL cholesterol, <0.001 for triglycerides, <0.03 for hemoglobin and 0.076 for age-adjusted fibrinogen. Chi-square analysis statistical probabilities are <0.05 for smoking, <0.001 for vessel disease, <0.01 for previous myocardial infarction. Coronaries = coronary arteries.

cate network of multiple relations. This complexity is illustrated in our patients by several univariate relations that go beyond the usual associations among various lipids and coronary artery disease. These include relations among triglycerides and total cholesterol and HDL cholesterol levels, but especially total/HDL cholesterol, and the relation of rheologic factors to clinical variables such as smoking, diabetes, hypertension and previous myocardial infarction. The relation of these clinical variables confirms the earlier suggestions of the importance of rheologic factors by Burch and DePasquale.[4]

With multivariate analysis, we also observed associations among total/HDL cholesterol, age, diabetes and gender with obstructive coronary artery disease. Characteristically, an elderly male diabetic with a high ratio is likely to have occlusive coronary artery disease.

Clustering: The strong relation between both HDL cholesterol levels and total/HDL cholesterol with the presence or absence of obstructive coronary disease has previously been emphasized in analyses of patients undergoing coronary arteriography.[1,22] Total/HDL cholesterol may offer the widest range of discrimination in identifying the extent of coronary obstructive disease.[1] The present study additionally proposes that total/HDL cholesterol may identify patients with clustering of high-level risk factors. This appears especially valid for men, although, despite a smaller group size and significant differences between men and women for several risk factors (Table I), clustering of high-level risk factors was also noted in women. It is likely that these variables act synergistically in groups and may thereby greatly contribute to the obstructive process in coronary arteries. A similar finding using the ratio—that risk factors at high levels tend to occur in groups—was noted in children in the Bogalusa Heart Study.[13]

Clinical implications: By itself, the ratio may represent the dynamic balance of cholesterol influx, by means of low-density lipoprotein cholesterol, and efflux, through a negative transport function of HDL cholesterol, from areas such as atherosclerotic plaque.[23] The additional identification by this ratio of persons with risk factors at high levels may strengthen the awareness of both patient and physician to the likelihood of obstructive coronary artery disease. The total/HDL cholesterol ratio may thus stand out as a marker that can be used to identify additional risk factors and that may result in a variety of treatments for this cluster of risk factors.

The percent decrease in HDL cholesterol levels is much greater than the percent increase in total cholesterol levels when moving from total/HDL cholesterol quartile 1 to 4. Greater emphasis on the importance of HDL cholesterol[22] associated with an only moderately elevated total cholesterol may therefore be required for the identification of the high-risk patient with a cluster of risk factors. Unfortunately, therapy for low HDL cholesterol levels is limited.[24] A larger number of options exist for the treatment of rheologic factors, such as fibrinogen or hemoglobin and hematocrit, with their closely related factor of viscosity. Anticoagulants, such as the coumarin derivatives, perhaps even in very low dosages,[25] aspirin, and fibrinogen-lowering agents, including pentoxifylline[26] and fish oil,[27] may have particular use, especially in patients in whom these factors are present at high levels and are clustered with other risk factors at high levels.

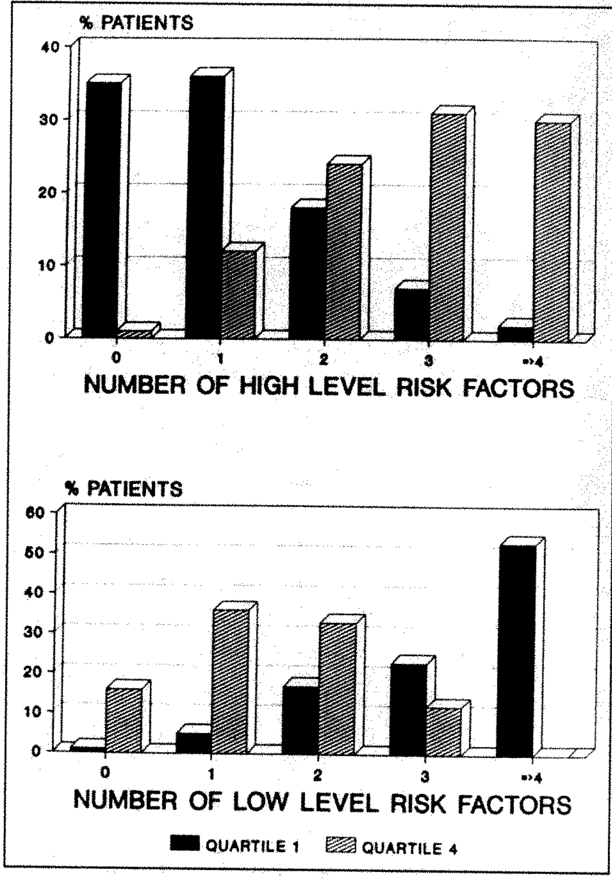

FIGURE 2. Quartile analysis of the ratio of total cholesterol to high-density lipoprotein cholesterol and risk factor clustering. The risk factors considered at high or low levels are total cholesterol, high-density lipoprotein cholesterol, triglycerides, hemoglobin, age-adjusted fibrinogen, smoking, previous myocardial infarction and number of coronary vessels with ≥50% obstruction. *Top*, a greater percentage of patients is noted to have ≥4 high-level risk factors in quartile 4 as compared with quartile 1 (p <0.001). *Bottom*, clustering of multiple low-level risk factors is demonstrated in quartile 1 in contrast to quartile 4 (p <0.001).

Recognition of clustering of high-level interrelated risk factors lends credence to the existence of a uniform background to coronary artery disease, whether or not the primary stimulus eventually proves to be genetic, dietary or environmental. For the clinician, moreover, the very fact that many risk factors tend to cluster at high levels adds greater insight to a clinical setting that so often appears abstruse.

Acknowledgment: We gratefully acknowledge the assistance of David Berg and Esther Luria.

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Prevalence of Unsuspected Mitral Regurgitation and Left Ventricular Diastolic Dysfunction in Patients with Coronary Artery Disease and Acute Pulmonary Edema Associated with Normal or Depressed Left Ventricular Systolic Function

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To define the prevalence and role of left ventricular (LV) systolic dysfunction, LV diastolic dysfunction and mitral regurgitation (MR) in patients with acute pulmonary edema, 40 patients with coronary artery disease and acute pulmonary edema were prospectively evaluated within 36 hours of presentation. LV ejection fraction and 3 parameters of LV diastolic function were measured with radionuclide ventriculography, whereas MR was assessed with Doppler echocardiography. LV ejection fraction was normal in 11 (27%) and depressed in 29 (73%) patients. Moderate or severe MR without LV diastolic dysfunction was common and equally prevalent in patients with and without LV systolic dysfunction (33 vs 38%; difference not significant). Diastolic dysfunction without MR was less frequent but equally prevalent in patients with and without systolic dysfunction (17 vs 27%; difference not significant). Two (18%) of 11 patients without and 12 (33%) of 36 patients with LV systolic dysfunction had both MR and LV diastolic dysfunction. Furthermore, MR was clinically silent and unsuspected in two-thirds of all patients with MR, regardless of a normal or depressed systolic function. These data show that there is a high prevalence of unrecognized moderate to severe MR in patients with acute pulmonary edema, regardless of the presence or absence of LV systolic dysfunction. Furthermore, the prevalence of LV diastolic dysfunction without MR is relatively low even in patients with normal LV systolic function and pulmonary edema. Thus, unrecognized MR may be an important contributor to the syndrome of acute pulmonary edema in patients with normal or depressed LV systolic function.

(Am J Cardiol 1991;67:37–41)

The clinical syndrome of acute cardiogenic pulmonary edema is usually associated with systolic dysfunction of the left ventricle, but recent studies have identified patients in whom pulmonary edema and heart failure are associated with normal or near normal left ventricular (LV) systolic function. These patients have been assumed to have primary LV diastolic dysfunction resulting in an abnormal relation between diastolic pressure and volume.[1-3] Most studies of such patients have been plagued with selection bias, inconsistent definitions of target groups and retrospective analyses of nonconsecutive series of patients.[1-5] In addition, in many of the reported studies, diastolic function was not directly measured,[1,3] or was determined days to months after the diagnosis of heart failure or pulmonary edema.[2] Furthermore, the potential importance of mitral regurgitation (MR) in patients with pulmonary edema and normal systolic function has not been clarified. To better define the prevalence of LV systolic dysfunction, diastolic dysfunction and MR in patients with acute pulmonary edema associated with coronary artery disease, 40 patients were studied with radionuclide ventriculography and Doppler echocardiography.

METHODS

Study design: Patients with acute pulmonary edema were evaluated upon presentation at Cedars-Sinai Medical Center by 1 of 3 investigators (GS, BG, PKS). Pulmonary edema was defined as a clinical syndrome of acute respiratory distress associated with radiographic evidence of interstitial or alveolar pulmonary edema. Patients were excluded if they were in cardiogenic shock or were unwilling or unable to consent to noninvasive testing. In addition, given the marked dependence of diastolic filling on the RR interval, patients with atrial fibrillation or marked ectopy were also excluded. Over a 7-month period, 60 consecutive patients were thus identified for further evaluation; of these, 20 were excluded—7 because of prior bypass surgery, 3 because of lack of evidence of coronary artery disease, and 10 be-

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cause of technical difficulties. Clinical information, obtained from patients and their attending physicians, when necessary, was supplemented with review of medical records. Electrocardiograms, chest x-rays and laboratory data were carefully reviewed, and the treatment provided and the hospital course closely followed.

Radionuclide ventriculography: All patients underwent radionuclide ventriculography within 12 hours (mean ± standard deviation 5 ± 3 hours) of presentation to the hospital. Data acquisition and analysis of ventricular function were modified from the technique of Bonow and Bacharach.[6] After intravenous injection of 25 mCi of in vitro labeled autologous red blood cells, equilibrium radionuclide ventriculography was performed using a high-resolution collimator, with imaging in the "best septal" left anterior oblique views. Analysis of global systolic and diastolic function was performed from the "best septal" left anterior oblique view, for which 40 frames per cycle were obtained with +5% cycle-length windowing, acquiring 200,000 counts per frame. The LV region of interest was meticulously chosen to exclude the left atrium, pulmonary veins and right ventricle throughout the cardiac cycle. After the background region of interest was chosen, a high-resolution time-activity curve was generated.

Left and right ventricular ejection fractions were calculated by computer analysis of the time-activity curves. In our laboratory, the normal mean ± standard deviation LV ejection fraction is 62 ± 7%.

For assessment of LV diastolic function, a third-order polynomial was fit to the peak ejection and peak filling phases of the time-activity curve by a least-squares technique. A quadratic polynomial was fit to the end-systolic portion of the curve. End systole was chosen as the data point closest to the nadir of the quadratic polynomial. The time to peak filling rate was measured as the time from end systole to the time of peak filling, chosen as the point where the second derivative of the peak filling polynomial was equal to zero. Stroke counts per beat were measured as end-diastolic minus end-systolic counts. The peak filling and peak ejection rates were then determined by calculating the first derivative of their respective polynomials (Figure 1). Peak filling rate was expressed in LV counts per second normalized to peak ejection rate and stroke counts. Peak filling rate thus normalized is independent of systolic function, unlike peak filling rate normalized to end-diastolic counts.[6,7]

Thus, 3 indexes of diastolic function were generated from each time-activity curve: peak filling rate normalized to stroke counts per second, peak filling rate divided by peak ejection rate, and time to peak filling rate expressed in milliseconds. These parameters were validated in our laboratory (Table I). At our institution, normal values for the indexes of diastolic function are peak filling rate, 4.03 to 9.63 stroke counts per second; peak filling rate/peak ejection rate, 0.81 to 1.21; time to peak filling rate, 104 to 180 ms. Diastolic dysfunction was said to be present if ≥2 of these indexes were abnormal. A representative time-activity curve from a patient with pulmonary edema is shown in Figure 2.

Echocardiography and Doppler examination: All patients underwent M-mode and 2-dimensional echocardiography and Doppler examination within 36 hours of enrollment. Studies were interpreted by 2 echocardiographers (GM, RS). Echocardiography and Doppler examination were performed with an IREX Meridian unit equipped with a dual frequency transducer that performs imaging at 3.5 MHz and Doppler at 2 MHz. The studies were recorded on both ½″ VHS videotape and stripchart paper. Examinations were done from the parasternal, apical, subxiphoid and, when feasible, suprasternal and right parasternal windows. Measurements of chamber sizes and wall thickness were obtained using standard American Society of Echocardiography criteria.[8] All 4 cardiac valves were examined with both continuous wave and pulsed Doppler echocardiography.

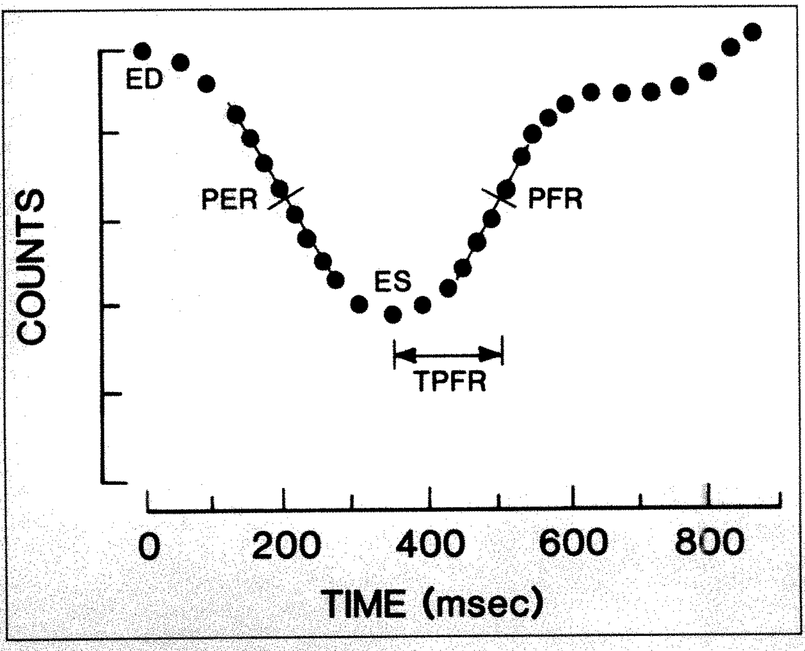


FIGURE 1. A representative normal left ventricular time-activity curve derived from radionuclide ventriculography. ED = end diastole; ES = end systole; PER = peak ejection rate; PFR = peak filling rate; TPFR = time to peak filling rate.

If MR was present, its extent was mapped in multiple planes. The degree of MR was semiquantitatively described based on the percentage of the cross-sectional area of the left atrium occupied by the regurgitant jet as follows: mild MR, 1 to 20%; moderate MR, 21 to 40%; severe MR, >40%.[9,10] For the purpose of this study, MR was considered present only it it was at least moderate or severe.[10,11]

Statistical analysis: Reproducibility of parameters of diastolic function (Table I) was assessed by the intraclass correlation coefficient.[12] A value of +1 indicates perfect reproducibility. Values greater than 0.8 indicate excellent reproducibility.

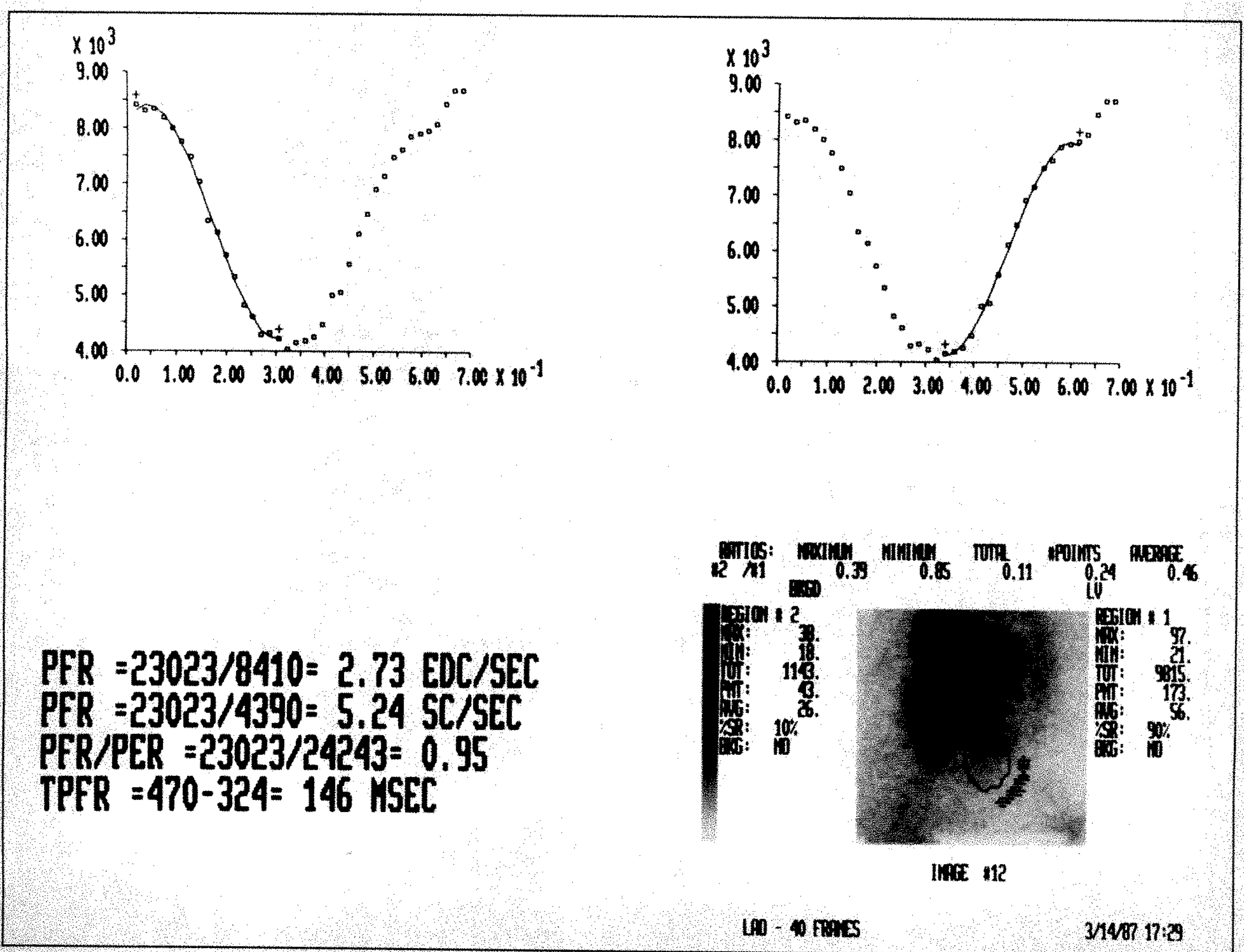
The distributions of the continuous variables were explored for the comparison subgroups of interest. In most cases the data were not normally distributed, or the variances were not equal between independent groups, or both. Therefore, the nonparametric Mann-Whitney U test was used to compare the distributions of 2 independent groups. All continuous variables were summarized by mean ± standard deviation. For categorical variables, independent proportions were compared using the chi-square test or Fisher exact test.

The α level of significance was set at 0.04 for all statistical tests. The stated p values are unadjusted for multiple comparisons. Because some comparisons were

TABLE I Normal Values and Reproducibility of Parameters of Diastolic Function Using Radionuclide Ventriculography

	Intraclass Correlation Coefficient			
	Intraobserver Reproducibility	Interobserver Reproducibility	Data Acquisition Reproducibility	Normal Values
PFR (EDC/s)	0.971	0.971	0.973	3.90 ± 0.74 (2.42–5.38)
PFR (SC/s)	0.963	0.988	0.852	6.83 ± 1.40 (4.03–9.63)
PFR/PER	0.934	0.875	0.957	1.01 ± 0.10 (0.81–1.21)
TPFR	0.987	0.935	0.927	142 ± 19 (104–180)

Mean values are ± standard deviation.
EDC/s = end-diastolic counts per second; PER = peak ejection rate; PFR = peak filling rate; PFR/PER = peak filling rate/peak ejection rate; SC/s = stroke counts per second; TPFR = time to peak filling rate.



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PFR =23023/8410= 2.73 EDC/SEC
PFR =23023/4390= 5.24 SC/SEC
PFR/PER =23023/24243= 0.95
TPFR =470-324= 146 MSEC
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RATIOS:   MAXIMUM   MINIMUM   TOTAL   #POINTS   AVERAGE
#2 /#1       0.39      0.85    0.11      0.24      0.46
          BKGD                           LV
REGION # 2                               REGION # 1
MAX:      38.                            MAX:    97.
MIN:      18.                            MIN:    21.
TOT:    1143.                            TOT:  9815.
PNT:      43.                            PNT:   173.
AVG:      26.                            AVG:    56.
%SR:    10%                              %SR:  90%
BKG:    NO                               BKG:  NO

                   IMAGE #12

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FIGURE 2. An actual left ventricular time-activity curve from a patient with pulmonary edema. Third-order polynomials are fit to the regions of the peak ejection rate *(upper left)* and peak filling rate *(upper right)*. EDC/SEC = end-diastolic count per second; LV = left ventricle; SC/SEC = stroke counts per second; other abbreviations as in Figure 1.

TABLE II Ventricular and Valvular Function in Acute Pulmonary Edema

	Normal Systolic Function (n = 11)	Depressed Systolic Function (n = 29)	p Value
% LVEF	55 ± 4	31 ± 8	<0.001
% RVEF	48 ± 6.5	42 ± 10	0.022
PFR SC/S	4.4 ± 1.4	5.1 ± 2.1	NS
PFR/PER	0.79 ± 0.27	0.96 ± 0.47	NS
TPFR (ms)	183 ± 62	183 ± 40	NS
Isolated MR (n)	6 (54.5%)	9 (31%)	NS
Isolated DD (n)	3 (27%)	5 (17%)	NS
MR + DD (n)	2 (18%)	10 (34%)	NS
Without MR or DD (n)	0	5 (17%)	NS

Mean values are ± standard deviation.

DD = diastolic dysfunction; LVEF = left ventricular ejection fraction; MR = moderate or severe mitral regurgitation; NS = not significant; RVEF = right ventricular ejection fraction; other abbreviations as in Table I.

TABLE III Prevalence of Mitral Regurgitation in Acute Pulmonary Edema

	Normal Systolic Function (n = 11)	Depressed Systolic Function (n = 29)	p Value
Total No. with MR (with or without DD)	8 (72%)	19 (65%)	NS
No. of MR patients with silent MR	7/8 (87%)	13/19 (68%)	NS
Overall prevalence of silent MR	7/11 (63%)	13/29 (45%)	NS

Abbreviations as in Table II.

based on very small sample sizes, nonsignificant results may reflect lack of statistical power. All computations were performed using BMDP statistical software.[13]

RESULTS

Clinical characteristics: The 40 patients in this study, 16 men and 24 women, with a mean age of 76 ± 8 years (range 52 to 96), all had underlying coronary artery disease; 28 (70%) had a history of systemic hypertension, whereas 15 (39%) had a history of diabetes mellitus. The diagnosis of coronary artery disease was made in all patients because of ≥1 of the following criteria: history of myocardial infarction (n = 18), coronary angiographic evidence of significant coronary artery disease (n = 8) or development of acute myocardial infarction during the current hospitalization (n = 15).

Ventricular and valvular function: LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION: For the purpose of analysis, patients were divided into 2 groups: those with normal LV systolic function and those with LV systolic dysfunction (Table II). Global systolic dysfunction was defined as LV ejection fraction <48%.

The mean LV ejection fraction was 43 ± 6% for the entire cohort of 40 patients, with 11 (27%) demonstrating normal LV systolic function and 29 (73%) demonstrating LV systolic dysfunction. Isolated diastolic dysfunction was present in 3 (27%) with normal systolic function, compared to 5 (17%) with systolic dysfunction (difference not significant).

MITRAL REGURGITATION: Moderate or severe MR with or without associated LV diastolic dysfunction was detected in 27 (67%) of the 40 patients, and the prevalence was comparable in patients with and without LV systolic dysfunction (65 vs 72%, difference not significant) (Tables II and III). Of these 27 patients with MR, a murmur of MR was entirely absent in 20 (74%), despite examination by multiple observers during the first 48 hours of admission. The prevalence of silent MR was comparable in patients with and without LV systolic dysfunction (68 vs 87%, difference not significant). Moderate or severe MR without LV diastolic dysfunction was present in 6 (54%) patients with normal LV systolic dysfunction, compared with 9 (31%) with LV systolic dysfunction (difference not significant). Combined LV diastolic dysfunction plus moderate or severe MR was observed in 2 (18%) patients with normal LV systolic function, compared with 10 (34%) with LV systolic dysfunction (difference not significant). Neither MR nor LV diastolic dysfunction was present in 5 of 29 patients (17%) with LV systolic dysfunction, compared with none of the patients with normal LV systolic function.

Hospital course: Fifteen (40%) patients had an acute myocardial infarction during the hospital course. LV dysfunction tended to occur more frequently in this group, compared with those who did not have an infarction (86 vs 64%). Complications (death, myocardial infarction, emergency revascularization) tended to be more frequent in patients with compared to those without systolic dysfunction (55 vs 18%, p = 0.08).

DISCUSSION

In this series of 40 patients with coronary artery disease and acute pulmonary edema, significant MR, which was frequently silent, occurred in 27 (67%) patients, and the prevalence of MR was comparable regardless of the presence or absence of LV systolic dysfunction. Whereas LV systolic function was normal in 11 patients (27%), isolated diastolic dysfunction was infrequent, occurring in only 3 (27%) of these 11 patients.

Comparison with previous studies: Using echocardiography and or radionuclide ventriculography, several authors have described normal global LV systolic function in 30 to 40% of patients with congestive heart failure of various etiologies.[1-5,14,15] Congestive heart failure in this subset of patients has generally been attributed to the presence of diastolic dysfunction, although direct indexes of diastolic dysfunction have rarely been determined.[1-5] In addition, the role of valvular dysfunction, particularly of MR, has not been previously addressed. In this study we attempted to overcome these limitations, studying 40 patients with coronary artery disease who presented with acute pulmonary edema, by using radionuclide ventriculography to assess LV systolic and diastolic function and by using Doppler echocardiography to assess MR. In this study, 11 (27%) of 40 patients had normal LV systolic function, a prevalence comparable to previous studies.[1,3] In addition, however, moderate or severe MR was common, occurring in 27 patients (67%), with a comparable prevalence in patients with and without LV systolic dysfunction (65 vs 72%, difference not significant). Of particular interest is the finding that MR was clinically silent and unsuspected in 20 (74%) of 27 patients. Of those with MR, the proportion with silent MR was comparable in patients with and without LV systolic dysfunction (68 vs 87%, difference not significant). Silent MR has not been specifically reported in patients with acute pulmonary edema, although it has been described previously in 39 to 57% of patients with acute myocardial infarction.[16] Although the overall 50% incidence of diastolic dysfunction (with or without associated MR) in this study is comparable to the 38% incidence reported by Soufer et al,[2] isolated diastolic dysfunction (without MR) was, however, rare, occurring in only 8 (20%) of 40 patients, with a comparable prevalence in patients with and without LV systolic dysfunction (17 vs 27%, difference not significant).

Methodologic issues and limitations: Radionuclide markers of LV systolic and diastolic function are influenced by loading conditions, inotropic state and heart rate. Thus MR may increase LV ejection fraction by its unloading effect while at the same time enhancing diastolic filling rate, thereby masking LV systolic as well as diastolic dysfunction.[17-20] In patients with a depressed LV ejection fraction, normalization of peak filling rate by the end-diastolic counts—the traditional way for expressing the peak filling rate—may result in an artificially depressed peak filling rate. To minimize this error, the peak filling rate was normalized to stroke counts in this study. Patients with irregular heart rate were not included to minimize the influence of varying heart rate on the indexes of diastolic function. No attempt was made to normalize the diastolic function to age, even though depressed diastolic function with normal aging has been reported.[21,22] Doing so, if anything, would have further reduced the number of patients considered to have a diastolic dysfunction beyond what is normal for their age. We further attempted to minimize the effects of therapy on the indexes of LV function by studying LV function soon after admission (mean, 5 hours) and before pulmonary edema had resolved; nevertheless, the use of diuretics and nitrates may have altered the loading conditions.

The degree of MR was semiquantitatively estimated and MR was considered to be present only when it was at least moderate or severe. Although the estimate of MR may have been influenced by the size of the left atrium, width of the regurgitant jet and the regurgitant orifice size, the severity of the MR assessed by this method correlates reasonably well with the angiographic estimates of MR severity.[11,23] Doppler studies were performed 6 to 36 hours after admission and many patients had improved by that time. This delay, if anything, however, might have led to an underestimation of the true prevalence of severe MR. The prevalence of silent MR was relatively high in this study. The high prevalence of silent MR cannot be solely explained by variability in the skill of observers, because silent MR was only diagnosed when none of the multiple physicians examining the patients during the first 48 hours (not only when the patients were severely symptomatic but also when they had recovered) had heard a precordial systolic murmur.

Conclusion: This study of patients with coronary artery disease and acute pulmonary edema found that, whereas approximately one-fourth of the patients had normal global systolic LV function, isolated diastolic dysfunction was uncommon in this subset. Significant MR was, however, present in the majority of patients with both normal or abnormal systolic function, was usually not detectable by auscultation, and may have contributed to the genesis of pulmonary edema.

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Ventricular Tachycardia and Accelerated Ventricular Rhythm Presenting in the First Month of Life

George F. Van Hare, MD, and Paul Stanger, MD

Fourteen infants aged <1 month presented to our institution during the last 22 years with ventricular tachycardia (VT) or accelerated ventricular rhythm and a structurally normal heart. In 2, VT was associated with long QT syndrome. Both are alive on β-blocker therapy, 1 with an implanted pacemaker. Twelve infants had accelerated ventricular rhythm, and 2 of these died in the first 2 months of life of unrelated conditions. The other 10 are alive at a median age of 4 years (range 2 months to 11 years), and none were lost to follow-up. Hemodynamic compromise did not occur with accelerated ventricular rhythm. The ventricular rate was very close to the sinus rate in all 12, <12% above the sinus rate. The mean QRS duration during accelerated ventricular rhythm was 92.5 ms, and averaged twice the QRS duration during sinus rhythm. Fusion beats were seen in all 12, and there was atrioventricular dissociation with capture beats in 10. In 2, ventriculoatrial conduction was present. Treatment was attempted in 5 of the 10 survivors with accelerated ventricular rhythm, and was thought to be successful in 4. Treatment was later successfully withdrawn in all 5, so that all 10 survivors were free of accelerated ventricular rhythm and were not receiving antiarrhythmic medications at last follow-up. Because of the excellent long-term outcome and the lack of hemodynamic compromise during the rhythm, it seems reasonable to withhold antiarrhythmic therapy in infants with accelerated ventricular rhythm and await resolution of the rhythm.

(Am J Cardiol 1991;67:42–45)

Ventricular tachycardia (VT) and accelerated ventricular rhythm are uncommon in children, and have been found to be due to a number of causes, including cardiac tumors,[1] myocarditis,[2] obstructive cardiac lesions,[3] electrolyte disorders[4] and antiarrhythmic therapy.[5] The prognosis depends on the cause, but VT has been shown to be associated with the development of ventricular fibrillation and sudden death, particularly when due to cardiac hamartomas[1] and prolonged QT syndrome.[6] These ventricular rhythms have only rarely been reported in the first month of life.[6–13] We report here our 22-year experience with VT and accelerated ventricular rhythm in neonates in the first month of life.

METHODS

We reviewed the records of all neonates with the diagnosis of sustained or nonsustained VT or accelerated ventricular rhythm at our institution from 1968 to the present. Hospital in-patient records, outpatient charts, electrocardiograms and 24-hour electrocardiographic tracings were reviewed. Follow-up information was obtained from referring physicians and family. Electrocardiograms demonstrating the arrhythmia were analyzed with respect to the following characteristics of the arrhythmia: QRS duration, fastest rate, slowest rate, tachycardia duration, QRS morphology, fusion beats, capture beats, atrioventricular dissociation or ventriculoatrial conduction.

RESULTS

Fourteen children presented within the first month of life with VT or accelerated ventricular rhythm and a structurally normal heart. They could be divided into 2 general groups: those with the prolonged QT syndrome presenting with polymorphous VT (n = 2), and those who presented with accelerated ventricular rhythm (n = 12). In all 14 patients, the occurrence of fusion beats in the absence of any signs of ventricular preexcitation indicated that the rhythm was ventricular in origin.

Group 1: Two neonates presented with polymorphous VT and prolonged QT intervals. The first patient has been previously reported,[6] and presented after delivery with nearly continuous, nonsustained polymorphous VT and with a QTc of 0.50 second during short runs of sinus rhythm. After an episode of ventricular fibrillation requiring cardioversion, she underwent implantation of an epicardial pacemaker for overdrive ventricular pac-

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TABLE I Accelerated Ventricular Rhythm

Pt No.	Age/Sex	Sinus Rate (beats/min)	Slowest Rate (beats/min)	Fastest Rate (beats/min)	QRS (ms)	QTc (s)	Age at Last Episode (d)	Age at Last Follow-Up (mos.)	Successful Medications	Unsuccessful Medications	Age Medications Discontinued (d)
1	20 d/M	142	150	200	90	0.47	20	2*			
2	24 hrs/M	130	136	136	90	0.45	1	4/30 d*			
3	14 d/M	181	187	200	90	0.37	1 d	31	Digoxin, propranolol		821
4	2 hrs/M	140	146	150	100	0.40	1	91	Propranlol		370
5	14 d/M	142	150	166	90	0.45	42	132	Propranolol, quinidine		365
6	3 d/F	167	187	200	80	0.38	4	90	Digoxin		360
7	1 hr/F	140	150	150	120	0.38	2	55		Lidocaine, propranolol	7
8	7 d/M	136	142	157	100	0.37	150	51			
9	1 hr/M	165	167	187	90	0.39	14	45	Digoxin		367
10	24 hrs/M	142	150	176	70	0.38	2	6†			
11	12 hrs/M	150	160	167	80	0.43	1	3†			
12	6 hrs/F	125	128	136	90	0.41	1	2†			
Mean ± SD			154.4 ± 18.72	168.9 ± 23.95	90.8 ± 12.4	0.407 ± 0.035					
Median 24 hrs							9	48‡			

* Died at this age due to unrelated conditions.
† Recent patients, currently being actively followed.
‡ Median age at follow-up of survivors, patients 3 through 12.
d = days.

ing at age 6 days. At age 8 months she is stable in a 100% paced rhythm with propranolol.

The second patient presented in 1968 at another hospital at age 5 hours with episodes of nonsustained polymorphous VT at rates of 230 to 350 beats/min. The episodes resolved and during sinus rhythm the electrocardiogram showed a QTc of 0.49 second. She was admitted to our medical center at age 1 month with a recurrence. The episodes were associated with hypotension and pallor. Treatment with propranolol, lidocaine, phenytoin and isoproterenol failed to control the arrhythmia. Therapy with digoxin was begun, which abolished the tachycardia. She was treated with digoxin until 6 months of age, when she was lost to follow-up. She reappeared at 3 years of age, when the diagnosis of long QT syndrome was made. Digoxin was stopped and she has been maintained on propranolol. At age 20 years, she was doing well, without attacks of tachycardia.

Group 2: The second group consisted of 12 infants who presented with accelerated ventricular rhythm and structurally normal hearts (Table I). All but 1 presented within 2 weeks of birth, often in the first hours of life. Echocardiography showed that all 12 had structurally normal hearts. One patient had a mildly decreased left ventricular shortening fraction. The episodes of accelerated ventricular rhythm were completely asymptomatic in all, and cardiac examination during the rhythm revealed no signs of hemodynamic instability.

Sinus rates were very close to the accelerated ventricular rhythm rates in all 12 patients (mean 95.1% of ventricular rate, range 89.3 to 98.8%). The QRS duration during accelerated ventricular rhythm was an average of 1.998 times the QRS duration in sinus rhythm. QRS morphology during accelerated ventricular rhythm was monomorphic in all. In 8, sufficient leads were recorded to allow an estimate of QRS mean frontal plane vector, which was right/inferior in 3, left/inferior in 4 and right/superior in 1. Fusion beats were found in all 12. Atrioventricular dissociation with capture beats of normal morphology were seen in 10 of 12, proving the ventricular origin of the rhythm (Figure 1). In 2 patients, ventriculoatrial conduction was intact (Figure 2). However, the episodes started with clear fusion beats in both, making the diagnosis of junction-

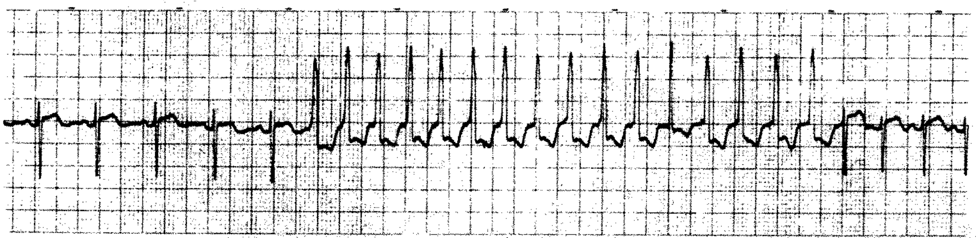

FIGURE 1. Patient 6, lead V_1 (see Table I). Note the onset of accelerated tachycardia rhythm at a rate slightly faster than the sinus rate, the evidence of atrioventricular dissociation, and the single capture beat (beat 12 after onset of rhythm) with a short QRS duration.

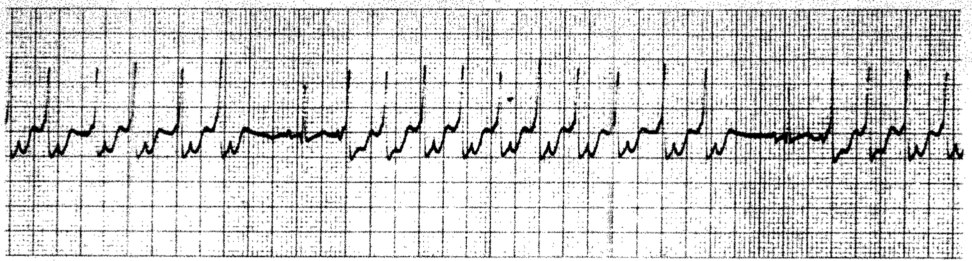

FIGURE 2. Patient 9, lead V_1 (see Table I). Note the fusion beat at the onset of accelerated ventricular rhythm and the appearance of retrograde P waves after the third beat of the ventricular rhythm.

al ectopic tachycardia with aberration very unlikely. Treatment was attempted in 5 of the 12 patients, and was thought to be successful, with complete suppression of the episodes of accelerated ventricular rhythm, in 4 patients. In all 5, medication was successfully withdrawn at a later date, with no recurrences.

Two of the 12 infants presented with accelerated ventricular rhythm and with severe illness. The first was a full-term neonate with an imperforate anus. After surgery, he developed a potassium level of 6.5 mg/dl and an osmolality of 233 mOsm/liter. During the infusion of 3% sodium chloride, he developed accelerated ventricular rhythm with a rate of 200 beats/min. The episode did not cause a change in clinical status and resolved spontaneously. He died at 2 months of age of severe graft-versus-host disease.

The second infant was born at 34 weeks' gestation and had trisomy 18, respiratory distress syndrome, necrotizing enterocolitis, and a patent ductus arteriosus that was ligated at age 3 days. At age 1 day, she had a cluster of episodes of accelerated ventricular rhythm at a rate of 135 beats/min. The episodes did not precipitate a change in clinical status, and the arrhythmia resolved spontaneously. She died at age 4 days of necrotizing enterocolitis.

All remaining 10 patients were healthy without receiving antiarrhythmic medications and were found to have had no arrhythmias at the last follow-up visit. Documentation of the lack of ventricular ectopy by 24-hour electrocardiographic monitoring in the absence of medication was available in 7 of the 12 patients.

DISCUSSION

We have found that infants who present in the first month of life with ventricular rhythms are a heterogenous group. True VT, presenting with more rapid ventricular rates and cardiovascular compromise, was rare, and in our experience was associated with prolonged QT syndrome. The largest group consists of those infants with structurally normal hearts presenting with accelerated ventricular rhythm, for whom the prognosis has been excellent. When accelerated ventricular rhythm occurs with simultaneous noncardiac disease, the prognosis appears to be related to the concomitant disease.

Accelerated ventricular rhythm occurs at rates similar to the sinus rates recorded just before and after the rhythm. The QRS duration is significantly longer than the normal QRS in sinus rhythm of a newborn, but is not long compared with normal adult QRS duration. Unlike the accelerated ventricular rhythm seen in older children and in adults, accelerated ventricular rhythm in the first month of life seems to be a phenomenon of the immediate newborn period, and disappears early in postnatal development.

Our data on accelerated ventricular rhythm confirm and extend earlier observations of several investigators, who have reported 17 cases in 8 well-documented re-

TABLE II Accelerated Ventricular Rhythm—Published Reports

Ref. No.	Age/Sex (d)	Sinus Rate (beats/min)	Ventricular Rate (beats/min)	QRS (ms)	QTc (s)	Age at Last Episode (d)	Age at Last Follow-Up (mos.)	Successful Medications	Unsuccessful Medications
Addy & Littlewood[4]	13/M*	145	180	100	0.34	13	2.5		
Hernandez et al[7]	1/F	—	166	110	—	75	7		Procainamide
Pedersen et al[9]	4/M	—	142	—	—	4	4		
Bergdahl et al[10]	3/M	—	194	—	—	3	5	Lidocaine, quinidine	
Bergdahl et al[10]	21/M	—	180	—	—	21	20		
Bissett et al[11]	1/M	140	140	—	—	3	6	Lidocaine, propranolol	
Bissett et al[11]	1/F	160	160	120	0.37	2	24		
Bissett et al[11]	1/M	140	140	100	0.39	1	6		
Geggel et al[12]	1/F†	170	188	90	"nl"	1	4.5		
Scagliotti et al[13]	1–2‡	—	120–175	—	—	2–14	1–120	Lidocaine	Lidocaine, propranolol
Eibschitz et al[14]	1/?	150	162	80	0.38	1	12		

* Associated with hyperkalemia: serum potassium concentration was 9.4 mEq/liter
† Associated with maternal cocaine use
‡ This line summarizes 8 similar patients.
"nl" = normal; Ref. = reference; ? = unknown; — = not provided.

ports[4,7,9-14] (Table II). These 17 cases represent the only well-documented cases of accelerated ventricular rhythm reported in neonates, and all had a benign course. Our own experience supports this benign prognosis. We provide a long follow-up interval for 7 of our 10 survivors. The remaining 3 survivors were born recently and are still being followed.

The benign nature of accelerated ventricular rhythm in neonates is similar to that reported in later childhood and in almost all adults. Gaum et al[15] reported 4 children, age 6 to 14 years, with accelerated ventricular rhythm. All 4 were asymptomatic during the rhythm, and it subsequently disappeared in all. In adults, accelerated ventricular rhythm has been defined as VT that occurs at a rate within 10 beats/min of the sinus rate.[16] It is a benign arrhythmia and has an excellent prognosis[16-19] with 1 exception. When it occurs within the first 24 hours after a myocardial infarction, there is a strong association with malignant ventricular arrhythmias.[20]

When a newborn infant presents with a ventricular rhythm, a differentiation should be made between VT and accelerated ventricular rhythm. In the latter, the rate is usually <200 beats/min and within 10% of the concomitant sinus rate, with no cardiovascular compromise. In contrast, in VT the rate is usually >200 and there are signs of cardiovascular compromise. Those with VT deserve a careful search for inciting factors, such as long QT syndrome, hamartomas and myocarditis, each of which requires specific therapy.[21]

Our experience, as well as that reported in this age group, suggests that attempts at suppressing accelerated ventricular rhythm with antiarrhythmic agents may be unsuccessful. Because of the excellent long-term outcome and the lack of hemodynamic compromise during the rhythm, one should withhold antiarrhythmic therapy in this group and await resolution of accelerated ventricular rhythm.

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Exercise Thallium-201 Imaging in Complete Left Bundle Branch Block and the Prevalence of Septal Perfusion Defects

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To determine the prevalence of septal defects in a generalized referral population, the records of 93 consecutive patients with complete left bundle branch block (BBB) who underwent symptom-limited treadmill exercise testing with thallium-201 myocardial imaging over a 3-year period were reviewed. Segmental analysis of the planar thallium-201 images was performed in a blinded fashion with agreement by consensus. Computerized quantitative analysis of the images also was independently performed, and was correlated with the visual interpretations. Forty-seven patients (51%) had normal images, and 46 (49%) had defects of ≥2 segments. In the abnormal studies, only 13 patients (14% of the total population) had septal defects, while a much higher number of patients, 33 (39%), had inferior or apical defects, or both. Coronary angiography was performed in 6 patients with septal defects: Significant narrowing of the left anterior descending coronary artery was found in 4 patients, a narrowed right coronary artery was found in 1, and normal coronary arteries were seen in the other patient. In conclusion, whereas previous studies have suggested a high percentage of false-positive septal defects in patients with left BBB, this study demonstrates a low prevalence (14%) of septal defects in a large population of unselected patients presenting for exercise thallium-201 imaging. Therefore, exercise thallium-201 imaging remains a useful procedure for evaluating patients with complete left BBB.

(Am J Cardiol 1991;67:46–49)

Thallium-201 imaging after exercise testing is recognized as the best clinically available noninvasive method for detecting significant coronary artery disease.[1,2] The test has been considered most important in patients with abnormal baseline electrocardiograms, such as bundle branch block (BBB).[3-5] Recently, use of thallium-201 imaging in patients with complete left BBB has been questioned due to an unusually high percentage of patients with septal defects in which subsequent catheterization demonstrated no evidence of disease in the left anterior descending coronary artery.[6-9] The high prevalence of false-positive septal abnormalities (range 14 to 100%) has led some investigators to suggest that thallium-201 scintigraphic evaluation of patients with left BBB may be misleading for the diagnosis of coronary artery disease.[8,9] However, the previous studies only evaluated patients in whom cardiac catheterization was performed because of symptoms and suspected left anterior descending artery disease, and the high percentage of septal defects may not be representative of a more generalized population in whom invasive procedures were not necessarily performed. Therefore, the purpose of the present study was to determine the prevalence of septal defects as well as other thallium-201 patterns in unselected, consecutive patients with complete left BBB referred for exercise testing.

METHODS

Patient selection: The records of all patients undergoing thallium-201 exercise testing at either The Miriam or Memorial Hospitals during the period January 1987 to March 1990 were reviewed. Electrocardiograms were evaluated by the investigators to confirm the presence of complete left BBB at rest and during exercise; such patients comprised the study population.

Exercise thallium-201 procedures: All patients completed a symptom-limited exercise test, utilizing the Bruce protocol. An intravenous injection between 2.2 and 3.0 mCi of thallous chloride was given 1 minute before cessation of exercise. Planar myocardial imaging was begun 5 to 10 minutes after completion of exercise, and was repeated approximately 4 hours later. Elscint or Phillips gamma cameras equipped with general, all-purpose, parallel-hole collimators were used for all studies. Images were obtained in the anterior, 30° and 70° left anterior oblique projections with ≥400,000 total counts per image.

Thallium-201 image analysis: Myocardial images were reviewed using a Sudbury Systems ImageCenter

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computer system and by ≥3 of the investigators. Identities of all studies were blinded and included images from patients without left BBB to assure impartiality. Agreement was by consensus, although any disagreement occurred in <10% of the studies.[10] To determine location of the defects, the heart contour on each projection was divided into 5 segments, for a total of 15 segments (Figure 1). Each segment was evaluated as having normal, diminished or absent photon activity. Any study was considered abnormal if ≥2 of the 15 segments were abnormal. Areas 6, 7, 11 and 12 were considered to represent the septal area. These areas were chosen because previous studies used these areas, and correlation of septal abnormalities by cardiac catheterization also has been made.[2,6-8] However, because areas 11 and 12 may also only reflect the anterior wall, no patient was categorized as having had a septal defect unless the abnormality included areas 6 and 7.

In addition to visual, blinded interpretation, the images were subjected to independent computerized qualitative analysis, using the procedure of Maddahi et al.[11] This program uses a circumferential profile analysis and compares the patient data with a group of 32 patients with a very low probability of significant coronary artery disease. Comparisons between the visual data and computerized analysis of the same images were made with regard to the presence and location of defects, and agreement was 95%. Discrepancies were resolved by either identification of artifact such as breast attenuation or by accepting the quantitative findings as correct.

Patients with thallium-201 abnormalities were further investigated with regard to subsequent coronary cineangiography, if performed within 3 months of the exercise testing. Significant coronary artery disease was considered present when luminal diameter narrowing of ≥70% was found in ≥1 major coronary artery.

RESULTS

Ninety-three consecutive patients (49 men and 44 women, mean age 66 years [range 37 to 81]) with complete left BBB at rest who underwent exercise thallium-201 testing during the study period were identified. Sixty-three patients had histories of chest pain, 23 reported prior myocardial infarction, 1 had a recent cardiac arrest and 10 were evaluated because of the presence of left BBB alone. No clinical data were available for 2 patients. Myocardial imaging revealed that 47 patients (51%) had normal and 46 (49%) abnormal studies. In the abnormal studies, only 13 patients (14% of the total population) had septal defects, whereas 33 had defects in other areas. The exercise characteristics of those with abnormal scans with or without septal defects were compared to those with normal scans. There was no statistically significant difference in the exercise duration, achieved percentage of the maximally predicted heart rate or the achieved heart rate-pressure product among the 3 groups of patients. Seven of 13 patients with septal defects achieved ≥85% of their maximally predicted heart rate.

The thallium-201 scans of the patients with abnormal studies were categorized into 5 regions: septal, anterior (not including the septum), inferior, apical and posterolateral (Figure 2). When each region was represented as a percentage of the total abnormal scans, a greater proportion of patients had either apical (74%) or inferior defects (54%) than septal abnormalities (28%). Some patients had >1 abnormal region.

Patients with septal defects were reviewed in detail (Table I). Chest pain was the primary reason for the exercise thallium-201 test in 8 of the 13 patients. The patients with septal defects showed evidence of ischemia by means of a reversible defect in all but 3 patients. Eight of the 13 patients also had defects in other areas, suggesting multivessel disease.

Coronary angiograms were available in 6 of the 13 patients with septal defects. Three-vessel disease with stenoses >75% in diameter was found in 1 patient, 95% narrowing of the left anterior descending artery was found in 3 patients, an isolated 99% stenosis of the right coronary artery was found in 1 patient, and normal coronary anatomy in 1 patient. Thus, ≥4 of the 13 patients with septal defects had disease consistent with the patterns of the scans. If one assumes that all 7 patients with septal defects who did not undergo cardiac cathe-

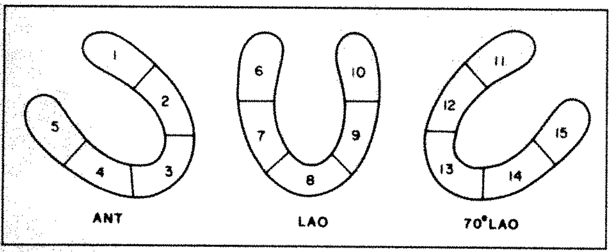

FIGURE 1. Evaluation of planar thallium-201 images. Each of 3 stress and delayed images (anterior [ANT], 40° and 70° left anterior oblique [LAO]) were subdivided into 5 segments, numbered 1 through 15. Each segment was judged normal or with reduced or absent photon activity. Stress and delayed images were compared for reversibility of defects. The abnormality must have been present in both segments 6 and 7 to be considered a septal defect.

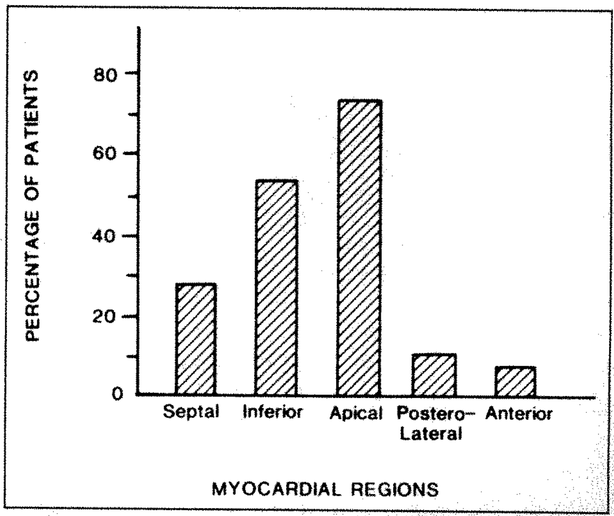

FIGURE 2. Location of thallium-201 imaging defects after exercise testing in patients with complete left bundle branch block. Each region is shown as the percentage of the total number of patients with abnormal scans. Some patients had multiple defects.

TABLE I Clinical and Angiographic Data in Patients with Septal Thallium-201 Defects

Pt. No.	Indications for Test	% MPHR	RPP	Area of Septal Tl-201 Defects*	Type	Area of Other Tl-201 Defects*	Type	Percent Narrowing by Angiogram Right	LAD	LC
1	CP	88	23,970	6,7,11,12	R	13,14	R	—	—	—
2	CP	84	26,040	6,7,11,12	R	3,4,5,8,13	R	—	—	—
3	LBBB	78	24,700	6,7	R	8,13	R	95	75	75
4	MI	61	15,680	6,7	F	3,4,5,8,14	F	99	0	0
5	CP	100	29,700	6,7	F	—	—	—	—	—
6	MI	80	14,880	6,7,11,12	R	2,3,13	R	0	95	0
7	CP	95	34,980	6,7,11,12	R	—	—	—	—	—
8	SH	72	25,200	6,7,12	R	3,4,8,13,14	R	0	95	0
9	PTCA, CP	86	23,800	6,7,11,12	R	3,8,13	R	0	95	0
10	CP	100	37,100	6,7,11,12	R	—	—	—	—	—
11	CP	102	29,004	6,7,11,12	R	—	—	—	—	—
12	CP	103	23,104	6,7,12	R	—	—	0	0	0
13	LBBB	78	21,648	6,7,11,12	F	8,13	F	—	—	—

* See Figure 1.

CP = chest pain; F = fixed defect; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LC = left circumflex coronary artery; MI = myocardial infarction; MPHR = maximal predicted heart rate; PTCA = percutaneous transluminal coronary angioplasty; R = reversible defect; RPP = rate-pressure product; Right = right coronary artery; SH = systemic hypertension; Tl-201 = thallium-201.

terization had no disease and were added to the 2 patients without left anterior descending disease who did undergo catheterization, a potential of only 9 of 93 patients could have had false-positive septal defects on exercise thallium-201 scintigraphy.

Eight of the 33 patients with abnormal scans in areas other than the septum also underwent cardiac catheterization, and all had evidence of obstructive coronary artery disease: 5 had multivessel disease, 2 had significant disease in the left anterior descending artery alone, and 1 had disease in the circumflex artery alone.

DISCUSSION

The present study evaluated 93 patients with complete left BBB presenting for exercise thallium-201 scintigraphy. We found that 51% had normal and 49% had abnormal studies. Thirteen patients (14% of the total population) in the abnormal study group had septal defects. Four patients with septal defects were found to have disease in the left anterior descending artery by cardiac catheterization, whereas 9 had either no disease in the left anterior descending artery distribution or were not studied. Thus, the overall incidence of septal defects in this unselected population was low (14%), and the false-positive rate was at maximum 10%.

Data from published reports have suggested an unusually high percentage of normal left anterior descending arteries in patients with left BBB and septal defects during exercise thallium-201 imaging. For example, Hirzel et al[6] reported on 19 patients with anteroseptal defects in whom coronary angiography was performed and found that left anterior descending coronary artery disease was present in only 21% of the patients, leaving 79% with normal coronary circulatory supply to the septum. Huerta et al[8] studied 11 patients with chest pain suggestive of coronary artery disease and left BBB who underwent coronary catheterization. Eight patients had septal defects and all 8 had normal coronary anatomy, whereas the remaining 3 had both normal thallium-201 scans and coronary arteries.

Depuey et al[9] also showed a high percentage (75%) of "false-positive" septal defects by thallium-201 single-photon emission computed tomography imaging. Interestingly, of their 14 patients with left BBB and abnormal thallium-201 scans, evidence for coronary artery disease by cardiac catheterization was found in 71% of patients, and reversible septal defects were associated with right coronary artery stenosis in 42% of patients (still considered false-positive). However, it may be argued that the septum can be supplied by the right coronary artery as well as the left anterior descending artery. In a study of 24 patients with left BBB by Braat et al,[7] only 1 of 8 patients with normal coronary arteries had a reversible defect in the septal area.

The findings in the previously discussed studies suggested that a high percentage of patients with septal defects have normal coronary anatomy in the distribution of that defect, causing concern over false-positive studies and the overall usefulness of the test. However, the prevalence of septal defects in patients with left BBB was not evaluated with the limited exception of Braat et al.[7] Another study by Rothbert et al[12] evaluated 74 patients with left BBB, but gave detailed information only on the 22 patients who underwent catheterization. They did report that 29% of their patients had normal scans.

The present study also demonstrates that the level of exercise achieved played no role in the development of septal defects, in contrast to the study of Depuey et al.[9] Patients in the present study with either normal or abnormal scans in other areas exercised to the same extent as did those with septal defects. In addition, the prevalence of septal defects in the group of patients who attained ≥85% of their maximal predicted heart rate was not different from that in the group of patients who did not reach 85%. Previous reports have speculated that the abnormal septal defects induced by exercise in patients with left BBB may be due to alteration in the pathway of septal electrical activation and propagation of the action potential.[13] However, this theory does not explain why 86% of our patients with left BBB had normal uptake of thallium-201 in the septum, or why there was not a greater percentage of defects in patients who exercised to higher energy levels. Thus, the etiology of septal defects in patients with normal coronary circulation remains speculative.

The present study was retrospective. Not all patients underwent cardiac catheterization, and the overall sensitivity and specificity for thallium-201 imaging in patients with left BBB could not be assessed. However, this was not the intent of the study; rather, the purpose was to assess the overall prevalence of septal abnormalities in a more generalized group of patients with left BBB. Had this study been confined to only those who underwent cardiac catheterization, patients with normal studies and many patients with abnormal scans in areas other than the septum would have been excluded because an invasive procedure was not performed or indicated. Had only catheterized patients been included in this study, the percentage of septal defects would have been 43%, not the 14% reported here.

The subjects evaluated in this study probably represent a general population of patients with left BBB and suspected coronary artery disease because only 49% of the patients had positive test results, and the pretest incidence of prior myocardial infarction was low (25%). In both this study and that of Braat et al, other abnormal thallium-201 perfusion patterns were found twice as often as septal defects.[7] In their study, all 12 patients with other defects were found to have significant coronary artery stenosis during cardiac catheterization. This also was true for the present study, although only a limited number of patients underwent catheterization. The contention in published reports is not whether defects in other areas represent coronary artery disease, but rather that the finding of a septal abnormality may represent a false-positive test. Our results do not refute that finding, but suggest that a much higher percentage of patients may have either normal scans or defects in areas other than the septum of the left ventricle.

Acknowledgment: We wish to thank Karen Poissant for excellent assistance in the preparation of the manuscript, as well as Andrea Rousseau-Devol and Deborah Messinger for excellent technical support.

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Characterization of Spontaneous Termination of Sustained Ventricular Tachycardia Associated with Coronary Artery Disease

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To characterize the change in cycle length and QRS morphology before spontaneous termination of sustained ventricular tachycardia (VT), electrocardiograms were recorded and VT cycle length measured for the periods 31 to 21 and 11 to 1 beats before termination in 55 episodes from 28 patients with coronary artery disease. Beats 31 to 21 were designated as a period of stable arrhythmia and served as a reference for changes occurring just before termination. Forty-four episodes of VT occurred in the setting of antiarrhythmic drug therapy; 11 episodes occurred in patients not treated with antiarrhythmic drugs. Variability in cycle length was indexed by the standard deviation of the mean cycle length and by the percentage of consecutive cycles varying by ≥40 ms (% ≥40 ms). There was greater variability just before termination (standard deviation of the mean cycle length, 25.8 ms; % ≥40 ms, 16.7%) than during the stable period (standard deviation of the mean cycle length, 8.5 ms; % ≥40 ms, 5.4%; p <0.001 for both). This was true irrespective of antiarrhythmic drug use, although the differences in the standard deviation of the mean cycle length for beats 11 to 1 and for beats 31 to 21 were greater for the antiarrhythmic drug group (29.6 vs 8.9 ms, p <0.001) than for the group not receiving antiarrhythmic drugs (11.0 vs 6.7 ms, difference not significant). No specific patterns of cycle length variability characteristic of VT termination were found. A change in QRS morphology occurred before termination in only 4 (7%) episodes of VT. In all, (1) cycle length variability increases immediately before spontaneous VT termination, although marked variability may occur without termination; (2) antiarrhythmic drugs may enhance the increase of cycle length variability at the time of termination; (3) distinct patterns of cycle length variability were infrequently seen at termination; and, (4) a change in VT morphology before termination is rare. These results may have implications for validating computer models of VT termination, for designing sensing criteria for antitachycardia devices and for increasing our understanding of antiarrhythmic drug action.

(Am J Cardiol 1991;67:50–54)

Cycle length variability and its relation to spontaneous termination of sustained ventricular tachycardia (VT) have not been described in humans. An association between an increase in cycle length variability and spontaneous termination has been noted in human supraventricular tachycardias[1-4] and in animal models of VT.[5,6] Studies of the effect of sudden changes in heart rate on ventricular conduction and refractoriness suggest that even modest changes in cycle length may have important effects on a reentrant circuit leading to arrhythmia termination.[7-11] In the present study, we characterized the changes in cycle length and QRS morphology that occur before spontaneous termination of sustained VT in humans, and determined the effect of antiarrhythmic drug therapy on the degree of cycle length variability.

METHODS

Patient group: Fifty-five episodes of sustained (>20 seconds), monomorphic VT that terminated without cardioversion or pacing intervention were analyzed. All episodes of VT were hemodynamically tolerated. The study group comprised 27 men and 1 woman, aged 37 to 79, with coronary artery disease and evidence of prior myocardial infarction (Table I). Mean ejection fraction was 26%. Episodes of VT were recorded during telemetry monitoring of in-patients (28 VTs), ambulatory Holter monitoring (10 VTs) and during electrophysiologic study (17 VTs) at recording speeds of 25 to 100 mm/s with 1 to 3 surface electrocardiographic leads. Episodes of VT recorded in the electrophysiology laboratory were induced with programmed stimulation; the onset of the remaining episodes was spontaneous. Eleven episodes of VT occurred in patients receiving no antiarrhythmic drugs, 37 episodes occurred in patients with "steady-state" antiarrhythmic drug levels, and 7 episodes were treated with acute intravenous administration of antiarrhythmic drugs (4 with lidocaine, 3 with procainamide and 1 with amiodarone). Multiple epi-

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TABLE I Patient Characteristics

Pt. No.	VT Episodes	Age (yr)	MI Location	EF	Antiarrhythmic Agent
1	4	72	AMI + IMI	32	proc (1), proc + lido (3)
2	1	72	AMI	30	amio + proc
3	2	41	AMI	31	amio (1), lido (1)
4	1	62	IMI	30	toc + proc
5	3	60	IMI	38	none (1), amio (1), amio + proc (1)
6	1	72	AMI + IMI	8	quin
7	1	68	AMI + IMI	22	amio
8	1	68	IMI	16	amio
9	5	70	IMI	40	none
10	5	76	IMI	15	none
11	2	79	AMI	26	proc (1), amio + proc (1)
12	1	58	IMI	37	amio
13	2	48	AMI	29	amio (1), amio + mex (1)
14	2	60	AMI	20	amio
15	1	64	IMI	25	amio
16	1	56	IMI	41	proc
17	3	64	AMI	17	amio (1), amio + mex (1)
18	1	69	IMI	37	proc
19	1	37	AMI	38	proc
20	1	60	AMI	8	proc + lido
21	4	52	IMI	38	amio (3), amio + mex (1)
22	3	57	AMI	39	amio + dilantin
23	1	52	IMI	19	none
24	1	74	AMI + IMI	17	proc
25	1	62	AMI + IMI	13	amio + lido
26	1	59	IMI	30	amio + proc + mex
27	1	48	AMI	23	diso
28	4	68	AMI + IMI	17	amio + proc

Numbers in parentheses refer to the number of episodes on each drug regimen.
AMI = anterior wall myocardial infarction; amio = amiodarone; diso = disopyramide; EF = left ventricular ejection fraction; IMI = inferior wall myocardial infarction; lido = lidocaine; mex = mexiletine; MI = myocardial infarction; proc = procainamide; quin = quinidine; toc = tocainide; VT = ventricular tachycardia.

sodes of VT from the same patient were included for study in several instances, accounting for 39 episodes. Of these 39 episodes, 7 VTs had a different QRS morphology, 19 VTs occurred with different antiarrhythmic drug regimens, 18 VTs occurred on different days, and 17 VTs had a ≥10 beats/min difference in rate; none of these criteria applied to 12 episodes in 5 patients.

Data analysis: The cycle lengths for beats 31 to 21 and 11 to 1 before VT termination were measured with manual calipers. Maximum measurement error, which was defined as the maximum interobserver variability in the measured cycle length, was determined to be ≤20 ms at the slowest recording speeds. The period of 31 to 21 beats before termination, chosen because it is a period of stable tachycardia, provided a reference point for changes that might occur immediately before termination. Cycle length variability was quantified in 2 ways (Figure 1): (1) calculation of the standard deviation of the mean cycle length over each period (beats 31 to 21 and 11 to 1) and (2) calculation of the percentage of consecutive cycles that differed by ≥40 ms (>2 × maximum interobserver measurement error). Specific patterns of cycle length variability at termination were described by comparing the cycle length of the last 4 beats of VT with the mean cycle length for beats 31 to 21; long and short cycles were defined as ≥20 ms above

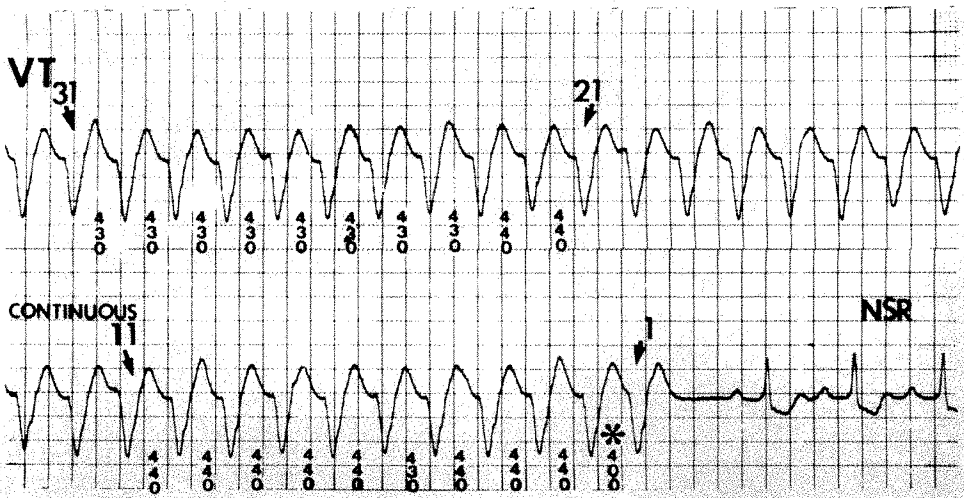

FIGURE 1. Representative example of spontaneous ventricular tachycardia (VT) termination with the intervals between beats 31 to 21 and 11 to 1 indicated *(arrows)*. Mean cycle length was 435.0 for 31 to 21 beats and 432.0 for 11 to 1 beats. The standard deviation of the mean cycle length was 12.8 ms for beats 31 to 21 and 4.2 ms for beats 11 to 1. * = 1 interval during beats 31 to 21 varied by ≥40 ms. NSR = normal sinus rhythm.

and below the mean, respectively. A change in VT morphology at the time of termination was defined as a distinct change in the QRS complex observed in ≥1 of the monitored leads.

Statistical analysis: Comparisons of paired observations (i.e., beats 31 to 21 vs beats 11 to 1) were made with Student's *t* test. Analysis of variance was performed to compare differences between drug-treated and non-drug-treated groups. A p value <0.05 was considered statistically significant. Data are reported as mean values ± standard error of the mean.

RESULTS

Relation of cycle length variability and tachycardia termination: Greater variation in cycle length occurred just before VT termination than during stable tachycardia (Figure 2, A and B). The standard deviation of the mean cycle length was 8.5 ± 1.6 ms for beats 31 to 21 and was 25.8 ± 3.9 ms for beats 11 to 1 before VT termination (p <0.001). The frequency of marked cycle length variability (≥40 ms change between consecutive intervals) showed a similar relation, with 5.4 ± 1.7% of the intervals for beats 31 to 21 and 16.3 ± 2.8% of the intervals for beats 11 to 1 (p <0.001). Of note, changes of ≥40 ms were observed in ≥1 interval in 15 (27%) of the 55 episodes of VT between beats 31 to 21 and in 29 (53%) of the 55 episodes of VT between beats 11 to 1. The range of cycle length variation for consecutive beats was up to 120 ms for beats 31 to 21 and up to 280 ms for beats 11 to 1.

Effect of antiarrhythmic drug therapy on cycle length variability: Cycle length variability increased before VT termination irrespective of antiarrhythmic drug therapy. However, antiarrhythmic drug therapy appeared to enhance the degree of cycle length variability at the time of termination (Figure 3A). In patients not treated with drugs, the standard deviations of the mean cycle length for beats 31 to 21 and for beats 11 to 1 were 6.7 ± 2.1 ms and 11.0 ± 2.4 ms, respectively (p = 0.085), whereas, for patients treated with antiarrhythmic drugs, the standard deviations of the mean cycle length were 8.9 ± 2.0 ms for beats 31 to 21 and 29.6 ± 4.7 ms for beats 11 to 1 (p <0.001). Similarly, the percentage of consecutive cycles differing by ≥40 ms was 4.0 ± 3.1% for beats 31 to 21 versus 7.0 ± 2.7% for beats 11 to 1 for the untreated patients (difference not significant) and was 5.8 ± 2.0% for beats 31 to 21 and 18.7 ± 3.4% for beats 11 to 1 (p <0.001) for patients receiving antiarrhythmic drug therapy. The mean change in standard deviation for beats 31 to 21 and 11 to 1 for each VT episode was significantly greater (p =

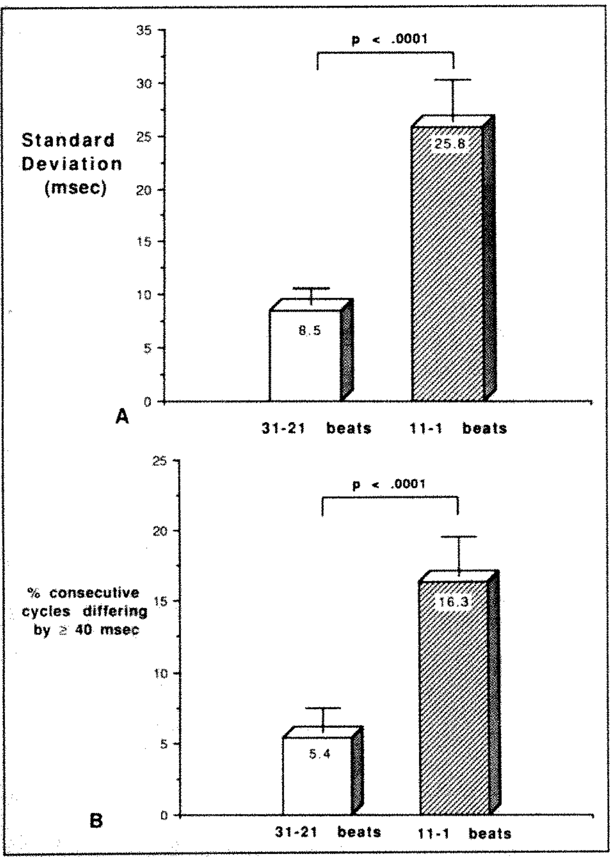

FIGURE 2. ***A,*** **the increase in cycle length variability just before ventricular tachycardia termination as measured by increase in the standard deviation of the mean cycle length and** ***B,*** **by the percentage (%) of consecutive cycles differing by ≥40 ms.** ***Open bars*** **represent 31 to 21 beats and** ***dotted bars*** **11 to 1 beats.**

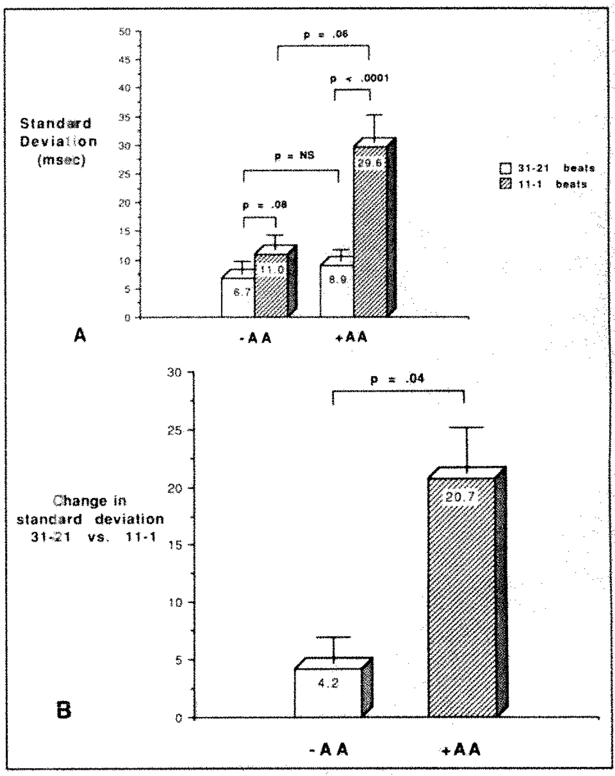

FIGURE 3. ***A,*** **the relation between antiarrhythmic drug use and cycle length variability. Variability was significantly greater before termination only in drug-treated patients.** ***Open bars*** **represent 31 to 21 beats for both nontreated (−AA) and antiarrhythmic drug-treated (+AA) groups.** ***Dotted bars*** **represent 11 to 1 beats for both groups.** ***B,*** **mean change of the standard deviation of the ventricular tachycardia cycle length during beats 31 to 21 and 11 to 1 for each ventricular tachycardia episode was significantly greater in the group treated with antiarrhythmic drugs (+AA) than the non-treated group (−AA). NS = not significant.**

0.04) in patients treated with antiarrhythmic drugs (20.7 ± 3.9 ms) than in those not treated with drugs (4.2 ± 2.2 ms, Figure 3B).

Further stratification of the patients treated with antiarrhythmic agents—into those who received acute intravenous drug therapy initiated during the VT episode and those maintained on a chronic, steady-state antiarrhythmic drug regimen—showed no difference between the 2 subgroups. For the patients receiving acute intravenous drug therapy, the standard deviations for beats 31 to 21 and beats 11 to 1 were 1.1 ± 1.1 ms and 31.1 ± 11.1 ms, respectively ($p = 0.034$); whereas, for the patients receiving chronic drug therapy, the values were 10.1 ± 2.2 ms and 29.3 ± 5.2 ms, respectively ($p < 0.001$).

Patterns of cycle length variability at the time of termination: No specific patterns of cycle length variability occurred with great frequency in this study. Examples of some patterns of cycle length variability noted at the time of VT termination are shown in Figure 4. A sudden shortening of the cycle length, preceded by 3 normal intervals, was the most frequent pattern of cycle length variability, and was seen only in 5 of 55 episodes. Many different patterns were observed, some terminating with short (12 VT) and some with long (17 VT) cycles. Of note, no apparent change (>20 ms) in cycle length (4 normal intervals) was seen in 14 of the 55 episodes immediately before termination.

Multiple episodes of ventricular tachycardia in the same patient: Although 14 patients had multiple episodes of VT, only 3 had episodes while both receiving and not receiving antiarrhythmic drugs, precluding a direct assessment of the effects of antiarrhythmic drug therapy. The degree of cycle length variability in this subset of patients was similar to that seen in the whole study population. Patterns of cycle length variability before VT termination were seldom identical in episodes of VT from the same patient; the same pattern occurred at termination in 9 episodes from 4 patients.

Change in QRS morphology at the time of termination: A change in QRS morphology was identified in only 4 (7%) of the 55 episodes of VT at the time of termination. No change in the QRS morphology was identified during the 31- to 21-beat interval in this patient population.

DISCUSSION

This study demonstrates that cycle length variability increases immediately before the spontaneous termination of sustained VT in patients with coronary artery disease. The increase in variability is not accounted for by changes in QRS morphology; thus, changes in the intrinsic electrophysiologic properties of the myocardium responsible for the perpetuation of the arrhythmia, rather than a spontaneous ventricular depolarization or a supraventricular capture beat, are responsible for arrhythmia termination in most patients. Of note, we also found that the use of antiarrhythmic agents was associated with greater cycle length variability at termination and with a greater change from the baseline degree of cycle length variability at 31 to 21 beats. Finally, only rarely were specific patterns of cycle length variability seen in the last 4 beats before termination, reflecting either the chaotic and unpredictable nature of the changes in the electrophysiologic properties responsible for VT termination, or the insensitivity of surface electrocardiography in indexing the underlying change in the electrophysiologic properties leading to VT termination, or both.

The mechanisms responsible for the development of the observed cycle length changes are poorly understood. Of note, many of the active properties of car-

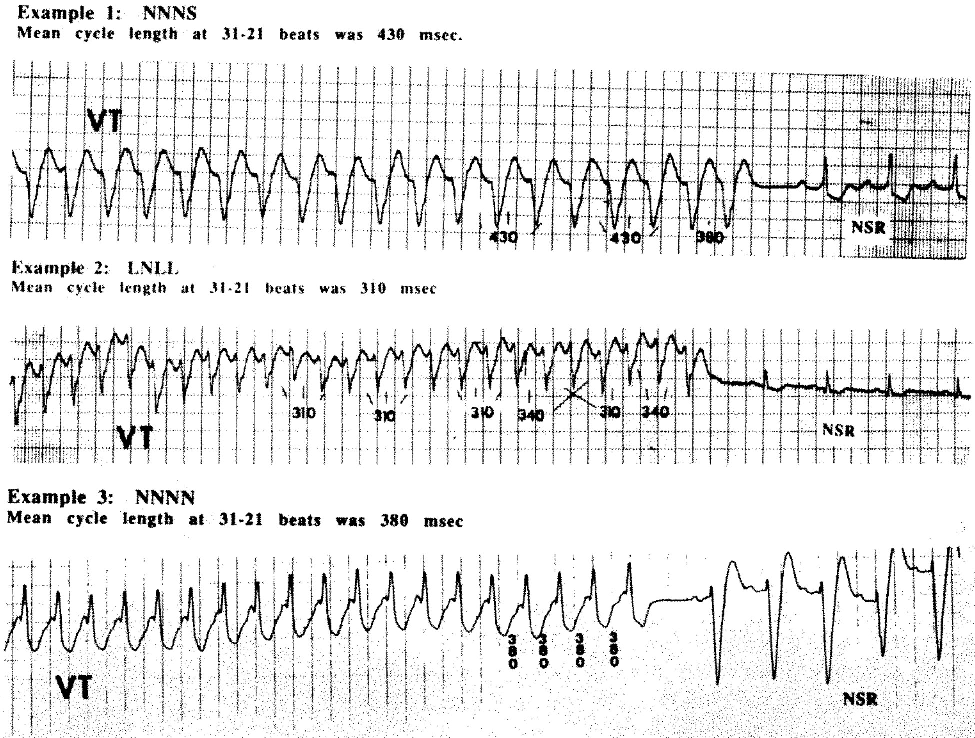
Example 1: NNNS
Mean cycle length at 31-21 beats was 430 msec.
VT
430
430
380
NSR
Example 2: LNLL
Mean cycle length at 31-21 beats was 310 msec
310
310
310
340
310
340
VT
NSR
Example 3: NNNN
Mean cycle length at 31-21 beats was 380 msec
380
380
380
380
VT
NSR

FIGURE 4. Several examples of patterns of cycle length variability at the time of termination. *Example 1* ends with an abrupt shortening of the cycle length (NNNS), a pattern seen in 7 of 62 episodes. *Example 2* terminates after cycle length prolongation (LNLL). *Example 3* illustrates ventricular tachycardia (VT) termination without any variability in cycle length (NNNN). L = ≥20 ms greater than the mean cycle length at 31 to 21 beats; N = within 20 ms of the mean cycle length at 31 to 21 beats; NSR = normal sinus rhythm; S = ≤20 ms less than the mean cycle length at 31 to 21 beats.

diac membranes are interval-dependent. The effects of abrupt increases in heart rate or premature stimulation on action-potential duration and refractoriness have been well characterized[7-9] and consist of an oscillatory change of these properties, with gradual dampening of the amplitude of the oscillation as new steady-state levels are approached. Simson et al[10] and, more recently, Frame and Simson[11] demonstrated that in order for a reentrant circuit to continue, it must be able to dampen spontaneous oscillations in conduction and refractoriness. Frame and Simson also observed that, although some degree of cycle length oscillation always occurred before termination, changes in diastolic interval were more critical for VT termination.[11] Because changes in diastolic interval are associated with reciprocal changes in action-potential duration, the oscillation in these parameters is greater than the oscillation in cycle length. This may explain why VT termination occurred in the absence of any cycle length changes in some of the patients.

The finding that antiarrhythmic agents further increased this variability in cycle length before VT termination is intriguing. Because most of the drugs used in this study have potent electrophysiologic effects on conduction and refractoriness, which may be cycle-length dependent, it is easy to conceive how they might make a reentrant VT less able to dampen oscillations in conduction, or refractoriness, or both, and thus potentiate tachycardia termination. Unfortunately, this study did not include a sufficient number of identical tachycardias from patients whose arrhythmias occurred both in the baseline state and while they were receiving antiarrhythmic drug therapy. Thus, our findings cannot be used to determine definitively the mechanism by which antiarrhythmic drug therapy enhanced the cycle length variability before VT termination or to distinguish between the effects of different classes of antiarrhythmic agents.

Finally, it is important to note that the degree of baseline variability of VT in the absence of termination was occasionally marked with variability in consecutive cycles of up to 120 ms. This information is important in establishing sensing criteria for the recognition of VT and for programming adaptive versus nonadaptive pacing modes for antitachycardia pacing. First of all, the degree of variability has been used as a diagnostic criterion for distinguishing VT from atrial fibrillation. The marked cycle length variability noted in our study during periods of stable tachycardia (27% of study population) may preclude the value of this sensing criterion in many patients. Second, the proper timing of a premature stimulus is essential for successful tachycardia termination.[12] As noted by Gerbel et al,[13] who studied cycle length variability in the first 100 beats of induced tachycardias, and by den Dalk et al,[14,15] a pacing algorithm that adapts to changes in cycle length on a beat-to-beat basis may obviate the potential problems that exist when cycle length variation is large and nonadaptive pacing modes are used.

Study limitations: The determination of the tachycardia cycle length with manual calipers and the recording of some episodes of VT termination at 25 mm/s limited the accuracy of our measurements. At this recording speed, interobserver reproducibility varied by a maximum of 20 ms. In addition, the use of only 1 to 3 surface electrocardiographic leads may have failed to identify a change in QRS morphology. Thus, the incidence of a change in the QRS morphology at the time of tachycardia termination may have been underestimated by this study. Also, the use of beats 31 to 21 before tachycardia termination to index baseline cycle length variability was somewhat arbitrary. Cycle length changes noted during this interval may not truly index steady-state variability and thus the degree of variability just before termination may have been underestimated. In addition, the inclusion of different episodes of VT from the same patient may have introduced a bias; however, we felt justified in treating each episode as a separate event, in that these episodes almost always occurred on different drug regimens or different days. Finally, the findings in this population may not apply to all instances of VT. The episodes of VT occurred in patients with coronary artery disease and were all hemodynamically tolerated. It is not known whether similar findings would be noted in other clinical settings.

Acknowledgment: We would like to thank Lateefah Shakir for skillful preparation of this manuscript.

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Duration of the QT Interval and Total and Cardiovascular Mortality in Healthy Persons (The Framingham Heart Study Experience)

Robert J. Goldberg, PhD, James Bengtson, MD, MPH, Zuoyao Chen, MD, MPH,
Keaven M. Anderson, PhD, Emanuela Locati, MD, and Daniel Levy, MD

The baseline electrocardiograms of 5,125 original subjects of the Framingham Heart Study were measured to examine the relation of the QT interval corrected for heart rate (QTc) to risk of total mortality, sudden cardiac death, and death due to coronary artery disease over a 30-year follow-up period. Quintiles of QTc (seconds) $\leq$0.36, 0.36 to 0.38, 0.39 to 0.40, 0.41 to 0.43 and $\geq$0.44 were studied in relation to these outcomes. There were no significant differences in the risk of total mortality, sudden cardiac death or death due to coronary artery disease according to QTc. A similar lack of significant association between QTc and these 3 outcomes was observed among all persons studied and in the 2 sexes after using a multiple regression analysis to control for several potentially confounding characteristics including age, gender, cigarette smoking, serum total cholesterol, systolic systemic blood pressure and Framingham relative weight. The results of this study fail to demonstrate an association between baseline QTc and overall mortality, and deaths due to sudden cardiac events or coronary artery disease in a large population-based cohort of essentially healthy persons in whom pathologic forms of QTc prolongation are uncommon.

(Am J Cardiol 1991;67:55–58)

Several conditions, including electrolyte imbalance, subarachnoid hemorrhage, mitral valve prolapse, selected drugs, and a congenital long QT syndrome have been associated with prolongation of the QT interval.[1–3] A prolonged QT interval has been associated with the occurrence of malignant ventricular arrhythmias during the hospital and postdischarge phase of acute myocardial infarction.[4–7] QT interval prolongation has also been associated with sudden cardiac death and an adverse long-term survival in patients with previous myocardial infarction[7–10] and in persons resuscitated from out-of-hospital ventricular fibrillation.[11] In 2 small studies of patients with acute myocardial infarction, a prolonged QTc was not associated with occurrence of either ventricular fibrillation[12] or serious ventricular arrhythmias.[13] A number of methodologic concerns arise, however, in the interpretation of these clinical series and hospital-based studies. These concerns include small sample sizes, use of inappropriate comparison groups, failure to control for potentially confounding factors of etiologic or prognostic significance and relatively short-term follow-up of patients with varying degrees of QT prolongation. The purpose of the present study is to examine the association of QT interval duration, corrected for heart rate (QTc) as recorded on the baseline entry electrocardiographic examination, with total mortality, sudden cardiac death and coronary artery disease mortality among the original cohort of the Framingham Heart Study.

METHODS

Patient population: The population under study consisted of the original cohort of 5,209 persons of the Framingham Heart Study who were between the ages of 30 and 62 years at the time of entry into the study in 1948.[14,15] The initial electrocardiogram of these persons was used to measure the duration of the QT interval, which was then adjusted for baseline heart rate (QTc) according to Bazett's formula.[16] The RR interval immediately preceding the QT interval was used in this formula. The average of 2 to 3 QT intervals from the electrocardiographic lead with the longest QT interval was analyzed.

The electrocardiograms of persons with coronary artery disease at the time of the baseline examination were excluded from study consideration as were the electrocardiograms of persons taking medications (e.g., antiarrhythmic drugs or tricyclic antidepressants) that

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TABLE I Baseline Characteristics According to Heart Rate–Corrected QT Interval (QTc): Framingham Heart Study

	Duration of QTc (seconds)				
	<0.36 (n = 499)	0.36–0.38 (n = 1,079)	0.39–0.40 (n = 1,464)	0.41–0.43 (n = 1,804)	≥0.44 (n = 279)
Age (yrs)					
<40 (%)	35	36	30	25	16
40–49 (%)	35	33	36	36	39
≥50 (%)	30	31	34	39	45
Male (%)	69	61	44	37	18
Current cigarette smoker (%)	60	60	52	47	39
Total cholesterol (mean, mg/dl)	227	227	226	228	230
Systolic blood pressure (mean, mm Hg)	132	133	134	133	134
Diastolic blood pressure (mean, mm Hg)	80	80	81	80	81
Framingham relative weight (% of normal weight)	102	102	103	102	103

might have affected the duration of the QT interval. Persons with missing baseline electrocardiograms were also excluded from further consideration. After these exclusions, a total of 5,125 persons remained and comprised the population of the present report. The primary study end points were defined as the following: total mortality (deaths from all causes); sudden cardiac death (onset of death within 1 hour of the onset of symptoms suggestive of acute coronary disease); and death due to coronary artery disease (persons dying from myocardial infarction, angina pectoris, or coronary insufficiency including sudden and nonsudden coronary events).

Each of the QT and RR intervals was measured manually by trained readers with the aid of calipers and magnifying lens. Ongoing quality control checks of the electrocardiograms were performed. These checks consisted of a weekly blinded duplicate review of a random sample of all electrocardiograms read during that time period by each of the observers. A high degree of inter- as well as intraobserver agreement was found and any discrepancies noted were subsequently adjudicated and corrected. In addition, a sample (n = 480) of these baseline electrocardiograms was independently and blindly reread 5 times by one of the study investigators (EL). A high degree of correlation was observed between the multiply read samples and the singly read baseline measurements with regard to the mean RR, average QT and QTc intervals (p <0.001).

Data analysis: Differences in the distribution of selected baseline characteristics between persons classified according to selected QTc intervals were examined through the use of chi-square and analysis of variance tests for discrete and continuous variables, respectively. A life-table approach was used to examine the risk of selected long-term mortality outcomes in relation to baseline QTc.[17] The log-rank test was used to assess the statistical significance of any observed overall differences in long-term outcome measures.[18] A Cox regression analysis was used to examine the relation of baseline QTc to various long-term end points while simultaneously controlling for the effect of several potentially confounding prognostic factors.[19]

RESULTS

Significant baseline differences existed between the various comparison groups with regard to age, gender and cigarette smoking status (p <0.05) (Table I). Persons with the more prolonged QT intervals included a significantly greater proportion of older persons, females and nonsmokers. A prolonged QTc (≥0.44 second) was observed in 5.4% of the persons studied.

Sex-specific analyses were also performed to examine differences in the distribution of selected coronary risk factors as well as QTc among the 2 sexes. Significant differences existed between the sexes with regard to systolic and diastolic blood pressure, smoking status and QTc. Men had significantly higher systolic (134.0 vs 130.6 mm Hg) as well as diastolic (81.3 vs 78.6 mm Hg) blood pressure and included a significantly greater proportion of current cigarette smokers (65 vs 42%) (p <0.001). On the other hand, women had a significantly longer mean QTc (0.401 ± 0.027 vs 0.385 ± 0.029 second) and QTc interval distribution (p <0.05). Among the men, 15% had a baseline QTc of <0.36 second, 29% a QTc between 0.36 to 0.38 second, 29% between 0.39 to 0.40 second, 25% between 0.41 to 0.43 second and 2% a prolonged QTc of ≥0.44 second. Among the women the distribution of these QTcs was 5% (<0.36 second), 15% (0.36 to 0.38 second), 29% (0.39 to 0.40 second), 43% (0.41 to 0.43 second) and 7% (≥0.44 second), respectively.

The association of QTc interval and all-cause mortality, sudden cardiac death and mortality from coronary artery disease was examined. No relation existed between duration of QTc and total mortality (Figure 1). Although not statistically significant, the greatest risks of dying were seen at the 2 most extreme QTc intervals examined.

In examining the association of QTc to long-term risk of sudden death (Figure 2), there were no significant differences observed in the risk of sudden death according to QTc. Trends toward an increased risk of sudden death were observed in persons with the shortest QTc (<0.36 second).

Similar to previously observed findings, there was no significant association observed between QTc and risk of dying from coronary artery disease in the cohort studied (Figure 3). Despite the lack of overall statistical significance, trends of increased death rates from coronary artery disease were seen in persons with the shortest baseline QTc.

A series of multiple regression analyses were then performed to examine the association of QTc to each of the 3 primary outcome measures while controlling for various potentially confounding demographic and coronary risk factor characteristics. The baseline variables adjusted for in these analyses included age, gender, cigarette smoking status, level of serum cholesterol, systolic blood pressure and Framingham relative weight. The results of these analyses confirmed previously observed univariate life-table findings, namely the absence of a significant association between duration of QTc and risk of total mortality, sudden cardiac death, and death due to coronary artery disease. The adjusted relative risks of these outcomes according to baseline QTc and accompanying 95% confidence intervals are listed in Table II.

Separate regression analyses for the 3 outcomes examined were also performed for the 2 sexes. The variables adjusted for in these analyses included age, cigarette smoking status, systolic and diastolic blood pressure, serum cholesterol level and Framingham relative weight. The results of these analyses were consistent with the previously observed summary findings of a significant lack of association between QTc and the selected outcomes examined. In both men and women, no significant association was seen between QTc interval and risk of either total mortality, sudden cardiac death and death due to coronary artery disease.

DISCUSSION

The results of this study suggest a lack of association between baseline QTc interval and overall mortality as well as mortality due to sudden cardiac events and coronary artery disease. The strengths of the present investigation include a large study population consisting of essentially healthy men and women originally enrolled in the Framingham Heart Study, long-term (30 years) follow-up, and use of various analytic approaches to examine the association of QT interval duration with selected study end points. The limitations of the study are that only the baseline electrocardiogram of the study population was used in relation to subsequent risk of selected

TABLE II Adjusted Relative Risk (RR) of Mortality from Selected Outcomes According to Duration of Heart Rate–Corrected QT Interval (QTc): Framingham Heart Study

	Adjusted RR of Mortality		
QTc (seconds)	Total*	Sudden Death	Coronary Artery Disease
<0.36†	1.0	1.0	1.0
0.36–0.38	0.80 (0.62, 1.04)‡	0.95 (0.57, 1.61)	0.96 (0.67, 1.40)
0.39–0.40	0.93 (0.72, 1.18)	1.15 (0.70, 1.89)	0.97 (0.68, 1.39)
0.41–0.43	0.93 (0.73, 1.19)	1.05 (0.63, 1.74)	0.97 (0.68, 1.39)
≥0.44	1.02 (0.70, 1.49)	1.31 (0.60, 2.86)	0.85 (0.48, 1.50)

* Adjusted risk of selected long-term outcome in relation to referrent category.
† Referrent category.
‡ 95% confidence intervals.

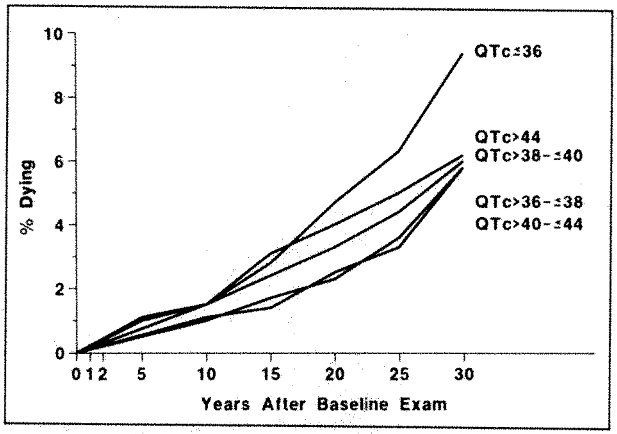

FIGURE 2. Cumulative risk of sudden death in the Framingham Heart Study.

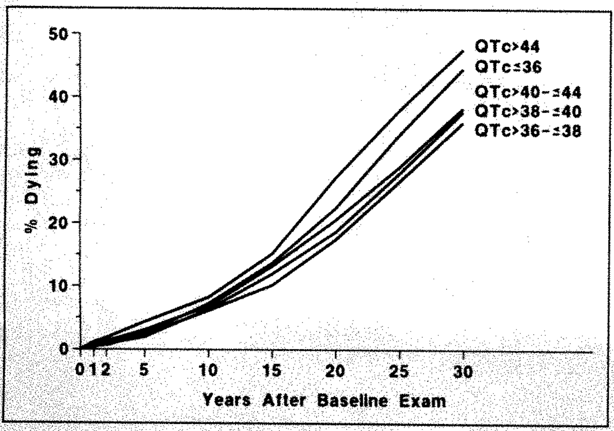

FIGURE 1. Cumulative risk of total mortality in the Framingham Heart Study.

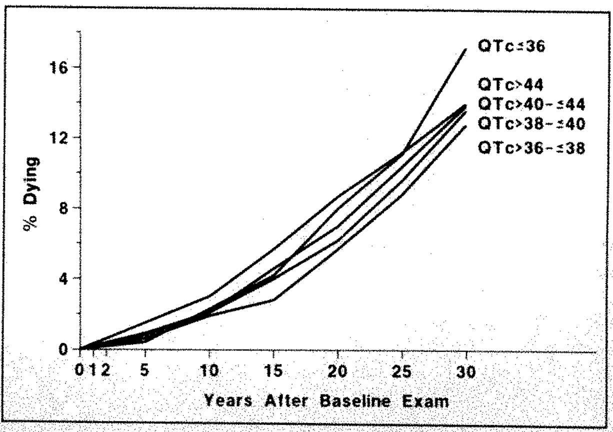

FIGURE 3. Cumulative risk of death from coronary artery disease in the Framingham Heart Study.

events and that changes in the QT interval may have occurred before the development of a cardiac event.

Previous studies examining the association of the QTc interval prolongation with risk of subsequent sudden or coronary death have primarily included patients with prior myocardial infarction,[7-10] those with out-of-hospital ventricular fibrillation[11] and persons with angiographically confirmed coronary artery disease.[20] Additional observational studies have examined the relation between prolongation of QTc interval and occurrence of serious ventricular arrhythmias in patients with acute myocardial infarction.[4-7] The consensus of these and other studies in patients with acute ischemic heart disease[21,22] is that increases in the duration of the QTc interval are frequently observed in patients during acute myocardial ischemia; increases in the length of the QTc are associated with an increased risk of sudden or coronary death in hospital survivors of myocardial infarction and in those resuscitated from out-of-hospital cardiac arrest. Measurement of the QTc interval in patients with documented coronary artery disease may, therefore, be of prognostic importance and of use in designing therapeutic interventions for such patients. The results of the present study suggest, however, a lack of association between QTc duration and risk of selected mortality outcomes in a large cohort of essentially healthy persons.

Acknowledgment: This study was made possible by the cooperation of members of the Framingham Heart Study staff and through the assistance of the medical director of this study, Dr. William Castelli. We are grateful for the preparation of this manuscript by Kelley Wall.

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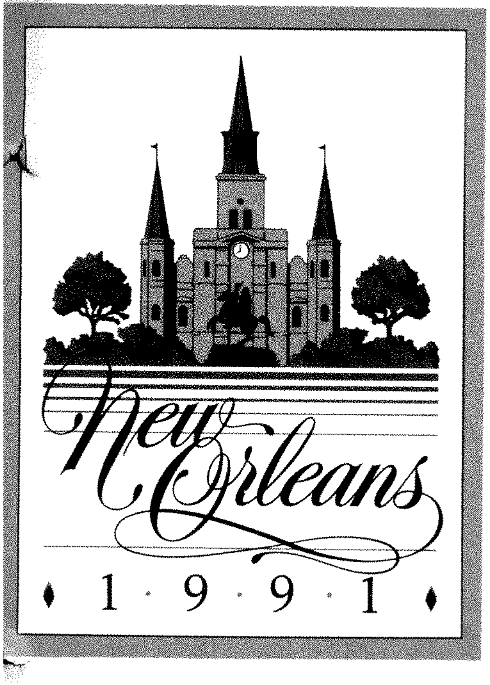

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Comparison of Lisinopril Versus Atenolol for Mild to Moderate Essential Hypertension

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The antihypertensive effects and safety profiles of lisinopril (10 to 40 mg) and atenolol (50 to 100 mg) were compared in a randomized, double-blind, parallel group trial in 144 patients with essential hypertension. After 8 weeks of therapy, seated blood pressure (BP) decreased by 26/15 mm Hg with lisinopril and by 19/14 mm Hg with atenolol. Lisinopril produced a greater reduction ($p < 0.05$) in sitting systolic BP than did atenolol. Standing BP decreased by 25/15 mm Hg with lisinopril and by 19/14 mm Hg with atenolol. No important changes in hematologic and biochemical profiles were seen with either drug. Eleven patients, 7 receiving lisinopril and 4 receiving atenolol, were withdrawn because of adverse experiences; another 3 patients defaulted during treatment, 1 in the lisinopril group and 2 in the atenolol group. Both drugs were well-tolerated and are therefore suitable for first-line therapy in essential hypertension.

(Am J Cardiol 1991;67:59–62)

Lisinopril (Carace®, Prinivil®, Merck, Sharp & Dohme, Zestril®, I.C.I.), an angiotensin-converting enzyme inhibitor, is effective in the treatment of essential hypertension[1-3] and congestive cardiac failure.[4,5] Comparative trials of lisinopril with hydrochlorothiazide,[1] nifedipine[2] and metoprolol[3] have shown that lisinopril is effective and well-tolerated. The antihypertensive activity of lisinopril when taken once daily has been shown to persist for 24 hours.[6] Atenolol (Tenormin®, I.C.I.) is a widely used cardioselective β-receptor blocker that can also be given once daily. This study compares lisinopril with atenolol in a large group of patients with essential hypertension.

METHODS

This randomized, double-blind, parallel group study was conducted in 8 centers throughout the United Kingdom. Patients were ≥18 years of age with a sitting diastolic blood pressure (BP) between 95 and 130 mm Hg (Phase V) after 2 weeks of placebo therapy. All were either newly diagnosed hypertensive patients or had previously received treatment that was ineffective or unacceptable because of adverse effects. Patients were excluded if they had evidence of myocardial infarction, angina, heart failure, stroke, malignant hypertension, or an underlying cause for their increased BP. Any contraindications to angiotensin-converting enzyme inhibition or to β blockade or evidence of clinically significant abnormal hematologic or biochemical profiles also excluded patients from entry. These included serum urea >10 mmol/liter, creatinine >150 μmol/liter, potassium outside the range of 3.2 to 5.2 mmol/liter, a white blood cell count <4,000/mm^3 or urinary protein excretion >1 g/24 hours. Informed consent from each patient and ethics committee approval for each participating center were obtained.

At initial evaluation, a complete physical examination and electrocardiogram were performed together with a full hematologic (hemoglobin, white cell count and platelets) and biochemical (urea, creatinine, sodium, potassium, urate, glucose, liver function enzymes) profile. Any antihypertensive therapy was then withdrawn and patients were then given supplies of matching placebo tablets of lisinopril 10 mg and atenolol 50 mg to be taken each morning. After 2 weeks on placebo tablets, patients returned to the clinic (week 0) and 2 measurements of BP were recorded with a Random

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TABLE I Patient Characteristics

	Lisinopril (n = 75)	Atenolol (n = 69)
Mean age (yr) ± SD	53 ± 13	55 ± 14
Range	23–85	22–85
Men/Women	40/35	38/31
Ethnicity		
Caucasian	60	63
Afrocaribbean	7	4
Indian-Asian	8	2
Duration of hypertension (mos.)		
Mean	53	47
Range	1–264	1–300

SD = standard deviation.

Zero Sphygmomanometer after 5 minutes sitting and 2 minutes standing. If the diastolic BP was within the range 95 to 130 mm Hg and all the inclusion criteria and none of the exclusion criteria were fulfilled, patients entered the 8-week active treatment phase. Patients were randomized initially to receive active lisinopril 10 mg with placebo atenolol or placebo lisinopril with active atenolol 50 mg, all tablets being taken in the morning. After 2 weeks of active therapy, patients in the lisinopril group with a sitting diastolic BP >90 mm Hg had the dose of lisinopril increased to 20 mg. Patients randomized to atenolol did not have a dose titration at this time. After a further 2 weeks, if the sitting diastolic BP remained >90 mm Hg, the dose of lisinopril was increased to 40 mg and the dose of atenolol to 100 mg and patients were reevaluated after a further 4 weeks. At each visit, BP, pulse rate and body weight were recorded and a residual tablet count performed. Hematologic and biochemical profiles were repeated at weeks 4 and 8.

Adverse events were sought out at each visit by standardized open questioning in which patients were asked whether they felt different in any way. Any symptoms were noted. The duration and severity of adverse events and the physician's assessment of any causal relations were recorded. Patients could be withdrawn from the trial because of side effects or lack of therapeutic effect at the discretion of the physician or at the request of the patient.

The study was designed to detect a 5-mm Hg difference in sitting diastolic BP between treatment groups ($p = 0.05$, power of 80%). Analysis was performed on changes from baseline and was conducted on the basis of an intention-to-treat analysis of all eligible patients. Results are presented with mean ± standard deviation and 95% confidence intervals. The significance of treatment comparisons is derived from between group *t* tests. Preliminary analysis of covariance to assess the possible influence of medical center, age, gender and baseline BP values indicated that these factors had very little affect on sitting diastolic BP.

RESULTS

One hundred forty-four patients (78 men and 66 women) entered the study, of whom 5 were protocol violators (sitting diastolic BP <95 mm Hg at entry). The characteristics of patients in terms of age, gender, race and duration of known hypertension for each treatment group were similar and are listed in Table I. The safety results are presented on all patients, whereas the efficacy results are presented on the 139 eligible patients. Seventy-one patients were randomized to receive lisinopril (mean BP ± standard deviation after 2 weeks of placebo, 170/107 ± 21/7 mm Hg sitting, 169/110 ± 20/10 mm Hg standing) and 68 to receive atenolol (mean BP after placebo 170/105 ± 21/7 mm Hg sitting, 168/109 ± 22/8 mm Hg standing). Ten patients (6 in the lisinopril group and 4 in the atenolol group) were withdrawn because of adverse experiences, which are discussed below. A further 3 patients defaulted during treatment (1 in the lisinopril group, 2 in the atenolol group). Of the eligible patients, 126 completed the study. Of the 5 protocol violators, 2 did not complete the study in the lisinopril group, 1 because of an adverse event; the other was withdrawn because of protocol violation.

BP and pulse rate data for each group at the end of the placebo period and at weeks 2, 4, and 8 are shown in Figure 1. Significant reductions in sitting and standing diastolic BP from baseline were comparable between

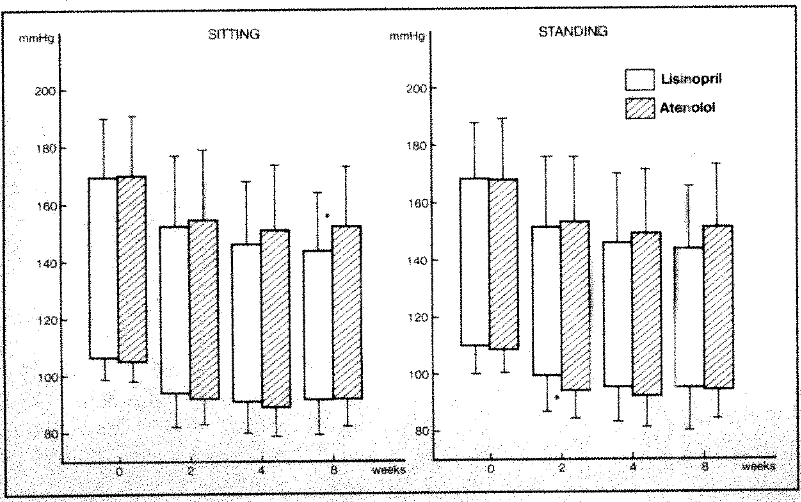

FIGURE 1. Mean values ± standard deviation for sitting and standing blood pressure at baseline and during 8 weeks of treatment with lisinopril or atenolol. All within-group changes were significant ($p < 0.05$). *$p < 0.05$ between-group comparison.

treatments and were apparent from week 2 (Figure 1). At week 8, for the sitting diastolic BP, a decrease of 15 mm Hg (95% confidence interval 12 to 18 mm Hg) was observed with lisinopril and 14 mm Hg (95% confidence interval 12 to 16 mm Hg) with atenolol. There was no significant difference in the change in diastolic BP between the 2 groups (p = 0.55). At week 8, a mean decrease in standing diastolic BP of 15 mm Hg (95% confidence interval 12 to 18 mm Hg) was observed with lisinopril and 14 mm Hg (95% confidence interval 12 to 16 mm Hg) with atenolol. No significant difference in the between-treatment comparison of mean changes was observed (p = 0.62). A significantly greater decrease in sitting systolic BP at week 8 was observed with lisinopril; 26 mm Hg (95% confidence interval 21 to 31 mm Hg) compared with atenolol; 19 mm Hg (95% confidence interval 15 to 23 mm Hg) (p = 0.02). The decrease in standing BP at the end of the study was also greater with lisinopril—25 mm Hg (95% confidence interval 20 to 30 mm Hg) compared with 19 mm Hg (95% confidence interval 15 to 23)—although this difference was not significant (p = 0.08). The target seated diastolic BP (≤90 mm Hg) was achieved at 8 weeks with lisinopril 10 mg in 17 of 22 (77%) patients, with lisinopril 20 mg in 10 of 21 (48%) patients and with lisinopril 40 mg in 3 of 21 (14%) patients. In the atenolol group, the target BP was achieved with 50 mg in 28 of 45 (62%) and with 100 mg in 6 of 17 (35%) patients. Both sitting and standing pulse rate decreased significantly in the atenolol group by 13 beats/min sitting (95% confidence interval 10 to 16 beats/min) and by 15 beats/min standing (95% confidence interval 11 to 18 beats/min), but no significant changes were seen with lisinopril.

Seven (9%) patients in the lisinopril group, including 1 protocol violator, and 4 (6%) patients in the atenolol group were withdrawn because of adverse experiences. In the lisinopril group, patient symptoms leading to withdrawal were single cases of dyspepsia, skin irritation, cellulitis of the hand, headache, cough, headache with nausea and headache with tiredness and numb feet. In only 4 of these patients were the events considered to be related to treatment. The symptoms leading to withdrawal in the 4 patients on atenolol were single cases of parasthesia with ankle swelling, skin rash, dizziness with nervousness, and syncope. In all 4 patients, physicians considered that the symptoms were possibly related to treatment. During the placebo period, 21 patients reported adverse experiences. During active treatment, 29 patients receiving lisinopril and 28 receiving atenolol reported adverse experiences dating back to the onset of active treatment. The most frequently occurring adverse experiences with lisinopril were headache (9%) and dizziness (7%). For atenolol, common adverse effects were dizziness (10%) and fatigue (7%) (Table II). Cough was reported by 2 patients taking lisinopril and by 1 patient taking atenolol.

TABLE II Most Common Adverse Experiences Reported During Active Treatment

	No. Pts. with ≥1 Occurrence		
Adverse Experience	Placebo (n = 144)	Lisinopril (n = 75)	Atenolol (n = 69)
Headache	6	7	1
Dizziness	2	5	7
Asthenia	2	3	5
Fatigue	0	1	3
Paresthesia	1	3	3
Cold extremities	0	0	4
Rash	0	3	1

No significant changes were observed in the hematologic or biochemical variables during the study. The results of serum potassium, urea and creatinine concentrations are listed in Table III. In 2 patients receiving lisinopril, serum potassium levels increased to 5.1 and 5.3 mmol/liter, respectively. Serum creatinine concentration increased from 93 to 156 μmol/liter in 1 patient receiving lisinopril. Serum urea concentration increased from 9.6 to 14.6 mmol/liter in 1 patient receiving lisinopril and from 8.7 to 10.7 mmol/liter in 1 patient receiving atenolol.

DISCUSSION

This study shows that lisinopril and atenolol significantly and equally reduced diastolic BP in patients with mild to moderate hypertension. A significantly greater reduction in sitting systolic BP was seen in the patients treated with lisinopril. Previous studies comparing lisinopril with atenolol,[7] and the other long-acting angiotensin-converting enzyme inhibitor, enalapril, with atenolol,[8] have shown similar effects on systolic BP. No significant changes in heart rate were observed during treatment with lisinopril. Whereas some vasodilators as well as diuretics have been shown to be associated with a reflex tachycardia, this has not been shown with angiotensin-converting enzyme inhibitors.[3,9,10] This lack of reflex tachycardia may be the result of increased vagal tone.[11]

TABLE III Mean ± Standard Deviation Serum Biochemistry Values at Baseline and After Eight Weeks of Active Treatment

	Lisinopril		Atenolol	
	Week 0 (n = 75)	Week 8 (n = 66)	Week 0 (n = 69)	Week 8 (n = 63)
Potassium (mmol/liter)	4.4 ± 0.4	4.5 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
Urea (mmol/liter)	5.5 ± 1.5	5.8 ± 1.2	5.1 ± 1.6	5.2 ± 1.1
Creatinine (μmol/liter)	93.7 ± 18.2	95.4 ± 19.8	91.6 ± 15.6	93.1 ± 15.1

Serum potassium levels were unchanged by either lisinopril or atenolol. A reduction of aldosterone secretion resulting from inhibition of the generation of angiotensin II may produce a small increase in serum potassium, although this was not seen here. Elevations in serum potassium to >5 mmol/liter occurred in only 2 patients receiving lisinopril, and serum creatinine and urea levels did not change significantly in either group.

Lisinopril and atenolol were well tolerated and the frequency of adverse experiences in each group or the frequency of withdrawal from the trial was comparable. Cough was reported by 2 patients who took lisinopril (3%) and resulted in the withdrawal of 1 of these patients. Cough is well recognized as a side effect of angiotensin-converting enzyme inhibitors, with a reported frequency in short-term studies between 0 to 3%.[12-14]

In conclusion, both lisinopril and atenolol produced a clinically useful reduction in BP, although lisinopril was more effective in reducing sitting systolic BP. The low incidence of both clinical and biochemical side effects suggest that lisinopril alone, like atenolol, may be of value in patients with mild hypertension.

Acknowledgment: We thank Nigel Freemantle for statistical support and Alison Chynoweth for secretarial assistance.

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Hemodynamic Effects of Renin Inhibition by Enalkiren in Chronic Congestive Heart Failure

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Previous efforts to block the renin-angiotensin system in patients with chronic congestive heart failure (CHF) have focused on 2 distal sites in the system, the angiotensin-converting enzyme and the angiotensin II receptor. Recent work, however, has led to the development of agents that directly inhibit renin, the proximal step in the cascade. In this study, we investigated the hemodynamic effects of renin inhibition in 9 patients with chronic CHF by using enalkiren, a primate-selective, dipeptide renin inhibitor, which has been previously shown to suppress plasma renin activity and to lower blood pressure in hypertensive patients. The acute intravenous administration of enalkiren (1.0 mg/kg) produced increases in cardiac index (2.0 ± 0.3 to 2.3 ± 0.1 liter/min/m^2) and stroke volume index (26 ± 3 to 34 ± 4 ml/m^2) and decreases in left ventricular filling pressure (31 ± 3 to 25 ± 3 mm Hg), mean right atrial pressure (15 ± 1 to 13 ± 2 mm Hg), heart rate (78 ± 5 to 72 ± 6 beats/min) and systemic vascular resistance (2,199 ± 594 to 1,339 ± 230 dynes·s·cm^{-5}) (all $p < 0.01$ to 0.05). These observations indicate that renin inhibition produces hemodynamic benefits in patients with chronic CHF and could potentially provide a novel approach to interfering with the renin-angiotensin system in patients with this disorder.

(Am J Cardiol 1991;67:63–66)

Activation of the renin-angiotensin system has been recognized as an important pathogenetic mechanism in patients with chronic congestive heart failure (CHF).[1] Previous efforts to block the system therapeutically have focused on 2 sites: the angiotensin-converting enzyme (the site of action of captopril, enalapril and lisinopril)[2] and the angiotensin II receptor (the site of action of saralasin).[3] The converting enzyme inhibitors are the only antagonists of the renin-angiotensin system that have achieved widespread acceptance by the medical community. Long-term treatment with captopril, enalapril and lisinopril produces sustained hemodynamic and symptomatic improvement and reduces the morbidity and mortality rates of patients with severe, chronic CHF.[2] These clinical benefits, however, may not be wholly related to the suppression of angiotensin II formation. Because the converting enzyme is identical to kininase II, the converting enzyme inhibitors act to retard the degradation of kinins, which may in turn exert vasodilator effects by a prostaglandin-dependent action.[4,5] Yet the importance of these non-renin mechanisms in mediating the beneficial effects of the converting enzyme inhibitors has been questioned,[6,7] and these non-renin mechanisms may underlie the development of cough and angioedema, 2 of the most troublesome adverse effects of these drugs.[8] Hence, it is possible that more specific antagonists of the renin-angiotensin system could provide most of the benefits of the converting enzyme inhibitors but with less risk.

A variety of compounds that inhibit renin (rather than the converting enzyme) have been synthesized during the last decade.[9,10] Because angiotensinogen is the only known substrate for renin, these agents specifically and selectively interfere with the renin-angiotensin system. Several renin substrate analogs that mimic the transition state of the renin-angiotensinogen complex have recently been tested in normal volunteers and hypertensive patients,[11-13] but the responses to renin inhibition in patients with CHF have not been evaluated. In the present study, we sought to examine the hemodynamic effects of renin inhibition in chronic CHF by using enalkiren (A-64662), a primate-selective, dipeptide renin inhibitor, which has been shown to suppress plasma renin activity and to decrease blood pressure in both monkeys and man.[13-17]

METHODS

Patient group: We evaluated 9 consecutive men (aged 39 to 81 years [mean 57]) with chronic CHF,

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who were referred for treatment with vasodilator drugs. The cause of CHF was coronary heart disease in 4 patients and idiopathic dilated cardiomyopathy in 5 patients. The left ventricular ejection fraction (measured by radionuclide ventriculography) ranged from 0.12 to 0.39 (mean 0.22). All patients had dyspnea or fatigue, or both, at rest or on minimal exertion despite treatment with digoxin (0.125 to 0.25 mg/day) and furosemide (40 to 320 mg/day), but were clinically stable at the time of evaluation. No patient had had an acute myocardial infarction within 2 months. All patients gave written, informed consent to participate in the study, which was approved by the institutional review board of the Mount Sinai School of Medicine.

For ≥5 days before the study, all patients maintained a salt-restricted diet and were treated with constant doses of digoxin and diuretics, but no vasodilator drugs. No patient had received a converting enzyme inhibitor, β-blocking drug or calcium channel blocker within the preceding 2 weeks. Right-sided cardiac catheterization and arterial cannulation were performed in all patients for the measurement of intracardiac and systemic pressures, respectively, using procedures that have been described previously.[18] All hemodynamic determinations were made the next morning (18 to 24 hours after right-sided cardiac catheterization) to allow for the dissipation of hemodynamic changes related to intravascular instrumentation.[18]

After the usual morning doses of digoxin and diuretics were withheld, mean arterial pressure, heart rate, mean pulmonary artery pressure, left ventricular filling pressure, mean right atrial pressure and thermodilution cardiac output were measured repeatedly (with a variation <10%) to ensure stability of the hemodynamic state before drug administration. Left ventricular filling pressure was estimated by the mean pulmonary capillary wedge pressure or as the pulmonary artery diastolic pressure after its identity with the wedge pressure was established. Patients then received incremental doses (0.003, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg) of enalkiren intravenously; each dose was administered as a bolus and was separated from the preceding dose by 45 minutes. All hemodynamic measurements were repeated 15 to 30 minutes after the 1.0 mg/kg dose of enalkiren.

Blood was collected for the measurement of plasma renin activity (by radioimmunoassay)[19] 5 minutes before the first dose of enalkiren and 10 minutes after the 1.0 mg/kg dose of the renin inhibitor. All blood samples were collected after patients had been supine for ≥4 hours.

Data analysis: Derived hemodynamic variables were calculated as follows: cardiac index = cardiac output/body surface area (liter/min/m^2); stroke volume index = cardiac index/heart rate (ml/m^2); systemic vascular resistance = 80 × (mean arterial pressure − mean right arterial pressure)/cardiac output (dynes·s·cm^{-5}); and pulmonary vascular resistance = 80 × (mean pulmonary artery pressure − left ventricular filling pressure)/cardiac output (dynes·s·cm^{-5}). Hemodynamic variables after enalkiren were compared with predrug values by the *t* test for paired data. Group data are expressed as mean ± standard error of the mean.

RESULTS

All 9 patients completed the study. Three patients reported transient flushing, but none experienced dizziness or lightheadedness.

Values for plasma renin activity were 8.4 ± 2.8 ng/ml/hour 5 minutes before enalkiren and fell to below the limit of detection (<0.2 ng/ml/hour) 10 minutes after the administration of the 1.0 mg/kg dose of the renin inhibitor. (These measurements of plasma renin activity after enalkiren should be viewed with caution, because the conventional radioimmunoassay for the measurement of plasma renin activity may no longer be valid in the presence of a renin inhibitor.[19])

Fifteen to 30 minutes after enalkiren (1.0 mg/kg), cardiac and stroke volume indexes increased by 17 and 32%, respectively, and mean arterial, left ventricular filling and mean right atrial pressures decreased by 13, 20 and 16%, respectively. Systemic vascular resistance decreased from 2,199 ± 594 to 1,339 ± 230 dynes·s·cm^{-5} (39%) and pulmonary vascular resistance decreased from 361 ± 59 to 249 ± 30 dynes·s·cm^{-5} (31%). Heart rate decreased from 78 ± 5 to 72 ± 6 beats/min. All hemodynamic changes were significant ($p < 0.05$ to 0.01) (Table I).

DISCUSSION

This report describes the first study to investigate the effects of renin inhibition in patients with CHF. Enalkiren, a primate-specific, dipeptide renin inhibitor, produced hemodynamic changes that might be expected to accompany the suppression of angiotensin II formation. Cardiac and stroke volume indexes increased, and right and left ventricular filling pressures, heart rate, and systemic and pulmonary vascular resistances decreased. The circulatory responses to renin inhibition were qualitatively similar to those that have been reported after converting enzyme inhibition with captopril, enalapril and lisinopril[20-22] and angiotensin II receptor blockade with saralasin.[3] The finding that hemodynamic improvement follows interference with the renin-angiotensin system at 3 different sites provides compelling evidence for an important role of this hormonal system in mediating the cardiovascular abnormalities of chronic CHF.

The development of enalkiren and other new renin inhibitors represents the culmination of many years of effort directed at discovering a means by which the activity of renin could be inhibited in the clinical setting. Early candidates in this field included phospholipids,[23] bacterial fermentation products such as pepstatin,[24] peptides related to the renin prosegment[25] and specific renin antibodies.[26] These approaches, however, were limited by poor solubility, lack of specificity and immunologic toxicity. Subsequently, analogs of the amino acid sequence around the cleavage site of angiotensinogen were shown to inhibit renin,[9] but these compounds could not be used for in vivo studies because of their low

TABLE I Hemodynamic Responses to Renin Inhibition in Chronic Heart Failure

Pt. No.		CI	SVI	MAP	MPA	LVFP	MRAP	HR	SVR	PVR
1	Pre	2.6	30	69	35	21	17	86	956	258
	Post	2.6	31	60	30	18	10	84	909	218
2	Pre	1.3	15	85	55	42	14	84	2,491	456
	Post	2.0	26	82	49	37	13	78	1,568	273
3	Pre	2.1	32	77	42	27	19	66	1,218	315
	Post	2.5	52	50	33	19	16	49	600	247
4	Pre	1.9	31	76	39	25	20	60	1,211	303
	Post	2.3	47	50	31	20	22	49	496	195
5	Pre	0.6	6	132	57	44	19	107	6,647	765
	Post	1.6	16	130	51	42	17	102	2,659	212
6	Pre	3.0	35	93	32	23	15	86	920	106
	Post	2.5	28	97	34	27	15	92	1,161	99
7	Pre	2.1	31	134	49	32	11	68	2,536	351
	Post	2.5	41	117	39	22	6	61	1,965	301
8	Pre	1.5	21	71	41	30	17	69	1,649	336
	Post	1.9	27	59	37	19	14	70	1,075	430
9	Pre	2.5	32	121	54	35	7	80	2,161	360
	Post	2.9	44	99	36	20	4	66	1,620	267
Mean	Pre	2.0	26	95	45	31	15	78	2,199	361
± SEM		±0.3	±3	±9	±3	±3	±1	±5	±594	±59
	Post	2.3	34	83	38	25	13	72	1,339	249
		±0.1	±4	±10	±3	±3	±2	±6	±230	±30
	p Value	<0.05	<0.02	<0.01	<0.01	<0.02	<0.05	<0.05	<0.05	<0.05

CI = cardiac index (liters/min/m^2); HR = heart rate (beats/min); LVFP = left ventricular filling pressure (mm Hg); MAP = mean arterial pressure (mm Hg); MPA = mean pulmonary artery pressure (mm Hg); MRAP = mean right atrial pressure (mm Hg); PVR = pulmonary vascular resistance (dynes·s·cm^{-5}); SEM = standard error of the mean; SVI = stroke volume index (ml/m^2); SVR = systemic vascular resistance (dynes·s·cm^{-5}).

potency. Recently, more potent analogs have been developed by replacing the dipeptide that contains the scissile bond of angiotensinogen with structures that resemble its configuration after activation for cleavage by renin.[10,11] This approach has resulted in a variety of novel compounds, of which enalkiren is 1 of a series of newly synthesized agents with a long duration of action. In both sodium-deplete and sodium-replete monkeys, enalkiren produces dose-dependent, short- and long-term decreases in blood pressure, which are accompanied by the near total inhibition of plasma renin activity.[14,15] The drug has also been shown to reduce plasma renin activity, angiotensin II and aldosterone in both normal and hypertensive volunteers and can decrease blood pressure in the clinical setting.[13,16,17,27] Our findings extend the favorable actions of enalkiren that have been reported in patients with hypertension to patients with chronic CHF.

Our patients with CHF showed consistent hemodynamic responses to enalkiren, whereas (despite similar inhibitory effects on the renin-angiotensin system) the hypotensive effects of the drug in normal volunteers and hypertensive patients have been variable.[13,16,27] Delabays[13] and Bursztyn[27] and their co-workers observed no consistent decrease in blood pressure in normal and hypertensive subjects, despite important decreases in plasma renin activity, plasma angiotensin II and plasma aldosterone; in contrast, we, Anderson et al[16] and Weber et al[17] observed notable decreases in blood pressure. These discordant findings may in part be related to differences in the dosage of enalkiren used in various studies. The highest dose employed by Delabays et al was only 0.1 mg/kg, whereas we and Anderson et al administered doses that were 10 times larger (1.0 mg/kg). Other data, however, fail to support the hypothesis that the dose of enalkiren is an important factor: Bursztyn et al[27] noted inconsistent antihypertensive effects even after a 1.0 mg/kg dose of enalkiren, whereas Weber et al[17] observed a decrease in blood pressure with only 0.1 mg/kg.

A more likely explanation for the different hemodynamic effects seen in published reports can be found by examining the sodium balance of the study patients. The 2 trials that showed little circulatory response to enalkiren evaluated subjects who were maintaining a normal sodium diet and were not taking diuretics[13,27]; the average plasma renin activity in these subjects was <1.0 ng/ml/hour. In contrast, the 2 studies[16,17] (in addition to the current report) that showed an important hemodynamic effect of enalkiren enrolled patients who were sodium-restricted, or taking diuretics, or both; the plasma renin activity was markedly elevated, exceeding 20 ng/ml/hour in some patients. The observations of Anderson et al[16] provide strong support for the importance of sodium balance. In this study,[16] low doses of enalkiren (0.03 mg/kg) were effective in reducing blood pressure in patients treated with a diuretic, but much larger doses (0.3 mg/kg) were needed to exert an antihypertensive effect in patients receiving no diuretic therapy. At any given dose, the hypotensive response to enalkiren was 2 to 3 times greater in patients receiving a diuretic than in those not treated with a diuretic drug.[16] Similar observations have recently been published by Weber et al.[17] Interestingly, the hemodynamic effects of both converting enzyme inhibitors and angiotensin-receptor antagonists in chronic CHF show a similar dependency on sodium balance,[3,28] presumably because sodium intake and excretion are major determinants of the activity of the renin-angiotensin system.

Although our data suggest that the effects of renin inhibition in chronic CHF are qualitatively similar to other means of interfering with the renin-angiotensin system, the current study was not designed to determine if the effects of renin inhibition and converting enzyme inhibition are quantitatively similar. The changes in left ventricular filling pressure that we noted during treatment with enalkiren appeared to be somewhat smaller than those reported with captopril, but they are similar to those observed with enalapril and lisinopril.[20-22] Some investigators, however, do not believe that these 2 ways of interfering with the renin-angiotensin system produce similar hemodynamic effects. Blaine et al[29] noted that renin inhibition produced no additional hemodynamic effects in sodium-deplete dogs pretreated with enalaprilat, but enalaprilat produced hemodynamic effects in dogs who were pretreated with a renin inhibitor. These investigators concluded that converting enzyme inhibitors exert hemodynamic effects unrelated to their interference with the renin-angiotensin system, perhaps as a result of their inhibitory effect on kinin degradation. Yet, other comparative studies indicate that renin and converting enzyme inhibition exert similar hemodynamic actions,[7,8] and at least one report suggests that renin inhibitors exert circulatory effects that may be additive to those of converting enzyme inhibitors.[30] Given these discordant observations, the controversy surrounding the relative efficacy of renin and converting enzyme inhibition in patients with chronic CHF will only be resolved by a direct comparative study.

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Effects of Bucindolol on Neurohormonal Activation in Congestive Heart Failure

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To examine the effects of β-adrenergic blockade on neurohormonal activation in patients with congestive heart failure, 15 men had assessments of hemodynamics and supine peripheral renin and norepinephrine levels before and after 3 months of oral therapy with bucindolol, a nonselective β antagonist. At baseline, plasma renin activity did not correlate with any hemodynamic parameter. However, norepinephrine levels had a weak correlation with left ventricular end-diastolic pressure ($r = 0.74$, $p < 0.01$), stroke volume index ($r = 0.61$, $p < 0.02$) and pulmonary vascular resistance ($r = 0.54$, $p < 0.05$). Plasma renin decreased with bucindolol therapy, from 11.6 ± 13.4 to 4.3 ± 4.1 ng/ml/hour (mean ± standard deviation; $p < 0.05$), whereas plasma norepinephrine was unchanged, from 403 ± 231 to 408 ± 217 pg/ml. A wide diversity of the norepinephrine response to bucindolol was observed with reduction of levels in some patients and elevation in others. Although plasma norepinephrine did not decrease, heart rate tended to decrease (from 82 ± 20 vs 73 ± 11 min^{-1}, $p = 0.059$) with β-adrenergic blockade, suggesting neurohormonal antagonism at the receptor level. No changes in I-123 metaiodobenzylguanidine uptake occurred after bucindolol therapy, suggesting unchanged adrenergic uptake of norepinephrine with β-blocker therapy. Despite reductions in plasma renin activity and the presence of β blockade, the response of renin or norepinephrine levels to long-term bucindolol therapy did not predict which patients had improved in hemodynamic status (chi-square = 0.37 for renin, 0.82 for norepinephrine). Thus, β-adrenergic blockade with bucindolol may reduce neurohormonal activation in congestive heart failure, but the reduction in plasma renin activity and norepinephrine may not predict hemodynamic improvement.

(Am J Cardiol 1991;67:67–73)

Congestive heart failure (CHF) is a disorder that produces reflex adrenergic stimulation as manifested by increased central sympathetic outflow,[1] elevation of plasma norepinephrine,[1-3] depletion of myocardial catecholamines,[4] and abnormalities in myocardial adrenergic norepinephrine uptake and release.[5-7] In the failing human heart, coronary sinus norepinephrine exceeds arterial levels,[5] suggesting net norepinephrine release by the heart. The primary defect in norepinephrine equilibrium appears to be decreased cardiac neuronal uptake per unit of interstitial space.[6] Because myocardial adrenergic norepinephrine uptake is decreased, norepinephrine spillover increases and augments sympathetic drive, despite the fact that myocardial tissue levels are decreased. In addition to activation of the sympathetic nervous system, the renin-angiotensin system is activated in CHF.[2] Elevations of both plasma norepinephrine[2,3] and plasma renin activity[2,8] have been suggested to be prognostically unfavorable, independent of ventricular function in patients with CHF.

Despite the beneficial effects of angiotensin-converting enzyme inhibitors,[9,10] plasma norepinephrine levels tend to continue to increase over time,[11] suggesting that reflex sympathetic activity is not attenuated long term by the hemodynamic improvement associated with these agents. Recently, other neurohormonal antagonists, β-adrenergic blockers, have been used for the treatment of CHF, with several small studies suggesting that chronic administration of β blockade may reduce mortality[12,13] and more recent studies indicating that β-adrenergic blockade improves ejection fraction, stroke work, end-systolic elastance and myocardial relaxation.[14,15] However, what effect β-adrenergic blockade has on neurohormonal activation in CHF is unclear. We therefore examined the effect of the β-adrenergic blocker, bucindolol,[14,15] on plasma renin activity and norepinephrine in patients with CHF. In addition, we performed quantitative tomographic scintigraphy with I-123 metaiodobenzylguanidine (MIBG), an agent that shares pharmacokinetic properties with norepinephrine.[16] MIBG and norepinephrine appear to share common uptake and

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storage mechanisms, and thus its uptake will reflect the status of adrenergic uptake of norepinephrine. Our hypothesis was that β-adrenergic blockade with bucindolol would reduce neurohormonal activation by improving hemodynamics and antagonizing renin and norepinephrine release.

METHODS

Patient group and study design: This study was done in conjunction with a comprehensive hemodynamic evaluation of the effects of bucindolol on left ventricular function in chronic CHF.[14] Fifteen men aged 32 to 62 years (mean ± standard deviation 50 ± 11) with New York Heart Association class I to IV CHF and a left ventricular ejection fraction <0.45 were studied before and after 3 months of chronic bucindolol therapy. Bucindolol was titrated weekly at the following doses: 12.5, 25, 50, 75 and 100 mg twice daily. Twelve patients had idiopathic dilated cardiomyopathy, and 3 had significant coronary artery disease to account for their left ventricular dysfunction, although none had evidence of a myocardial infarct within the preceding 2 months. Fourteen of the patients were taking angiotensin-converting enzyme inhibitors during the trial. No patient had a change in angiotensin-converting enzyme inhibitor dosage during the trial period or for 2 months before entering the trial. All medications remained constant during the study period except for diuretic drugs, which were altered as clinically indicated. Each patient gave written informed consent, and the protocol was approved by the Human Studies Subcommittee of the Dallas Veterans Administration and University of Texas Southwestern Medical Centers in December, 1987.

Plasma catecholamines and renin samples were obtained at baseline and after 3 months of bucindolol therapy. Plasma norepinephrine levels and MIBG scans were performed nearly simultaneously in a fasting state, within 10 days of cardiac catheterization. Plasma catecholamine samples were obtained after the patient remained in a supine position for 30 to 40 minutes through a heparin lock placed at the start of the rest period. The blood was immediately immersed in ice and centrifuged for 20 minutes at 2 to 4°C at 1,000 ± 100 g. Analysis was done by Smith, Kline, Bio-Science Laboratories (Van Nuys, California) using high-pressure liquid chromatography with electrochemical detection.[16] Plasma renin was obtained during an overnight supine state the morning of cardiac catheterization and placed on ice. Analysis was performed using a standard radioimmunoassay.

MIBG scintigraphy: MIBG radiopharmaceutical preparation was performed as previously outlined.[16] Lugol's solution, 1 ml, was given by mouth 30 to 60 minutes before MIBG injection. The patients were injected intravenously with 8 to 10 mCi of I-123 MIBG while in an upright position. Imaging was performed at 4 hours after injection. All imaging was performed using a dedicated 3-detector imaging system (PRISM 3000, Ohio Imaging, Bedford Heights, Ohio). MIBG projection images were acquired for 20 seconds each at 3-degree increments over 360° orbits and were recorded at a digital resolution of 64 × 64. Energy discrimination was provided by dual 20% windows centered over the 80 and 167 keV photopeaks of thallium-201 and a 15% window centered over the 159 keV photopeak of I-123.

MIBG image analysis: Transaxial tomographic sections from the I-123 MIBG images, including the entire cardiac volume, were reconstructed by filtered backprojection of the projection images acquired over the 180° anterolateral arc from the 45° right to 45° left anterior oblique position. The filter used during reconstruction was the product of a ramp and a Kaiser-Bessell filter (order of 5.0). Corresponding vertical long- and short-axis sections were selected from the reconstructed volumes. Representative vertical long-axis and apical, midventricular and basal short-axis sections of the left ventricle were selected for analysis of segmental I-123 MIBG activity.

I-123 MIBG tomograms were analyzed quantitatively in the following manner: Segmental regions of interest were placed over the most homogenous region of myocardial uptake as determined by 1 observer (AIM). A region was not selected if cardiac activity was either contaminated by or not separated from surrounding lung or liver activity. The method of region of interest determination was simple and easily reproducible. The average counts per voxel (counts/voxel) were corrected for millicurie injected dose and decay. The counts were assessed in a 2 × 2 pixel region from the center of the segment. This same segment was used for repeat analysis after β-blocker therapy.

Hemodynamic assessment: Patients underwent cardiac catheterization just before initiating therapy and after 3 months of bucindolol. Ten minutes after initiation of atrial pacing at 15 beats/min above the intrinsic heart rate, left ventricular function was assessed by digital ventriculography interfaced with simultaneous micromanometer pressure measurements. Intravenous nitroprusside was then administered to decrease blood pressure by 10 to 15% and repeated digital ventriculography was performed at multiple loading conditions. Left ventricular volumes were determined by a standard angiographic area-length method.[14] End-diastole applied to the largest ventricular volume (near the peak of the R wave) and end systole was taken as the smallest volume in each cardiac cycle. End-systolic elastance, a relatively load-independent index of contractility, was determined from analysis of left ventricular pressure-volume loops as previously described.[14] When patients returned to the catheterization laboratory after 3 months of therapy, the same procedure was used with care to match the original atrially paced heart rate used in the baseline study.

Reproducibility: Reproducibility of the plasma renin activity measurements were obtained by comparison of a known commercially available standard to 11 repeated-assay measurements in our laboratory. The standard activity was 4.1 ± 1.0 vs 3.8 ± 0.8 ng/ml/hour measured by our laboratory (difference not significant for repeated-measures analysis of variance). The reproducibility of the norepinephrine measurements has been made by Smith Kline Bio-Science Laboratory (Van

Nuys, California) with a coefficient of variation of $\leq 10\%$.

Statistical analysis: Renin and norepinephrine values and mean MIBG counts per voxel before and after bucindolol were compared by paired Student's *t* test. Hemodynamic and neurohormonal variables at baseline were compared by linear and second-order polynomial regression. A p value <0.05 was considered significant. All results are expressed as mean ± 1 standard deviation unless otherwise stated.

RESULTS

Hemodynamic and functional changes with bucindolol: All patients tolerated the titration of bucindolol well. Only 3 patients, 2 of whom had ejection fractions of <0.10, were unable to tolerate the maximal dose of 100 mg twice daily because of mild light-headedness, and were given 75 mg twice daily. Two of the patients had their diuretic dosage increased nominally during the 3-month trial period (from 80 to 120 mg orally twice daily).

The hemodynamic results of this trial have been previously published.[14] To summarize briefly, 7 of the 15 patients had functional class III or IV CHF at entry. There was an improvement in New York Heart Association functional class from 2.5 ± 0.8 to 1.8 ± 0.6 with β-adrenergic blocker therapy (Figure 1).

HEMODYNAMICS BEFORE PACING: Heart rates were mildly reduced with bucindolol therapy, but this did not reach statistical significance (82 ± 20 vs 73 ± 11 min^{-1}, $p = 0.059$). Both peak systolic pressures (109 ± 17 to 120 ± 26 mm Hg, $p = 0.023$), and aortic end-systolic (dicrotic notch) pressures (90 ± 12 to 98 ± 18 mm Hg, $p = 0.049$) increased with therapy. Left ventricular end-diastolic pressures decreased from 19 ± 8 to 15 ± 5 mm Hg ($p = 0.021$). Cardiac output increased from 5.0 ± 1.5 to 5.8 ± 1.6 liters/min ($p = 0.004$) but systemic vascular resistance did not change ($1{,}318 \pm 406$ to $1{,}183 \pm 290$ dynes·s·cm^{-5}, $p = 0.17$).

HEMODYNAMICS WITH ATRIAL PACING: There was a significant increase in left ventricular ejection fractions from 0.23 ± 0.12 to 0.29 ± 0.14 ($p = 0.0071$). This increase was due to a decrease in left ventricular end-systolic volumes from 100 ± 51 to 84 ± 51 ml/m^2 ($p = 0.0047$). The decrease in left ventricular end-systolic volumes and increase in ejection fractions occurred despite a decrease in left ventricular end-diastolic pressures and volumes (preload), and an increase in aortic end-systolic pressures (afterload). There was also a significant increase in end-systolic elastance from 0.60 ± 0.40 to 1.11 ± 0.45 mm Hg/ml ($p < 0.005$). Thus, filling pressures decreased, while contractility and functional class improved.

Correlation of baseline neurohumoral state and hemodynamics: Technically adequate supine plasma renin activity assays were obtained in 12 of the 15 patients and plasma norepinephrine was assessed in 11 of 15. Baseline plasma renin activity did not correlate with any baseline hemodynamic parameter, including left ventricular ejection fraction, left ventricular end-diastolic pressure, cardiac output, stroke volume index, end-systolic elastance, and pulmonary and systemic vascular resistances. Whereas baseline norepinephrine levels did not correlate with baseline systemic vascular resistance, end-systolic elastance and left ventricular ejection fraction, there were weak correlations with left ventricular end-diastolic pressure ($r = 0.74$, $r^2 = 0.55$, $p < 0.01$), stroke volume index ($r = 0.61$, $r^2 = 0.37$, $p < 0.02$), cardiac output ($r = 0.55$, $r^2 = 0.3$, $p = 0.08$) and pulmonary vascular resistance ($r = 0.54$, $r^2 = 0.29$, $p < 0.05$) (Figure 2).

Effects of bucindolol on plasma renin activity and plasma norepinephrine: Plasma renin decreased with bucindolol therapy from 11.6 ± 13.4 to 4.3 ± 4.1 ng/ml/hour ($p = 0.044$) (Figure 3). Plasma norepinephrine was unchanged from 403 ± 231 to 408 ± 217 ($p = 0.95$) with β blockade with bucindolol (Figure 3). A wide diversity of response to bucindolol was observed with reduction of norepinephrine levels in some patients and elevation in others. We arbitrarily defined improvement as 2 of the following 3 criteria: (1) an increase in end-systolic elastance of >0.2 mm Hg/ml, (2) an increase in left ventricular ejection fraction ≥ 0.05, and (3) an improvement in New York Heart Association functional class. The response of renin or norepinephrine levels to chronic bucindolol therapy did not predict which patients improved hemodynamically and functionally (chi-square = 0.37 for renin, 0.82 for norepinephrine). Thus, there was no correlation between modulation of norepinephrine or renin by bucindolol and hemodynamic improvement.

MIBG scintigraphy: Regional MIBG uptake was unchanged (from 56.6 ± 21.7 to 54.7 ± 23.2 counts per voxel, difference not significant) after bucindolol therapy.

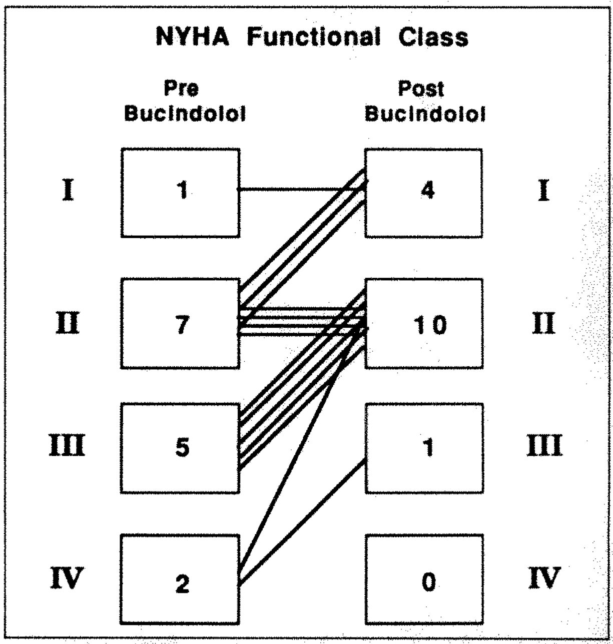

FIGURE 1. There was significant improvement in New York Heart Association (NYHA) functional class from 2.5 ± 0.8 to 1.8 ± 0.6 (mean ± standard deviation). The individual responses can be seen in this schematic diagram.

DISCUSSION

This study demonstrates that β-adrenergic blockade with bucindolol reduces plasma renin activity in patients with CHF while plasma catecholamines and MIBG uptake are not affected. One previous study suggested that administration of a β blocker with intrinsic sympathomimetic activity acutely lowers plasma renin activity.[17] However, in this previous acute intervention study, plasma renin activity was very low at baseline and decreased in 8 of the 10 patients who tolerated therapy, but increased severely in 2 patients who decompensated with β-blocker administration. Thus, for the 10 patients enrolled in this earlier study, the overall mean plasma renin activity increased with β blockade. Thus, our study is the first demonstration that long-term β-adrenergic blockade reduces plasma renin activity in CHF. Additionally, we observed weak correlations between baseline left ventricular end-diastolic pressure, stroke volume index, cardiac output, pulmonary vascular resistance and baseline plasma norepinephrine, suggesting a possible relation between hemodynamic decompensation and a low-output state with elevation of plasma norepinephrine.

Effects on the renin-angiotensin system: Suppression of renin release by β-adrenergic blockade may be a direct effect on β_1 receptors that mediate renin release[18] or a secondary phenomenon due to improved renal perfusion. As β_1-adrenergic stimulation has been shown to activate the renin-angiotensin system through renin release from the juxtaglomerular apparatus, β_1 blockade would be expected to reduce renin release.[18] All but 1 of these patients had pretreatment with an angiotensin-converting enzyme inhibitor before initiation of β blockade. Although converting enzyme inhibitors are known to increase plasma renin activity,[19] the baseline values reflect many stages of renin-angiotensin activation with values ranging from 0.14 to 36.9 ng/ml/hour. Although activation of the renin-angiotensin and sympathetic nervous system has previously been shown to be nonuniform in patients with CHF,[20] the reason for a lack of hyperreninemia in some patients taking converting enzyme inhibitors is not clear.

The lack of correlation of plasma renin activity and hemodynamic improvement is not surprising. Because 14 of 15 patients were taking angiotensin-converting enzyme inhibitors at the time of study, a correlation of renin activity with hemodynamic improvement may have been masked. Had the renin-angiotensin system not been blocked "downstream" before initiation of β blockade, a correlation might have been evident. Alter-

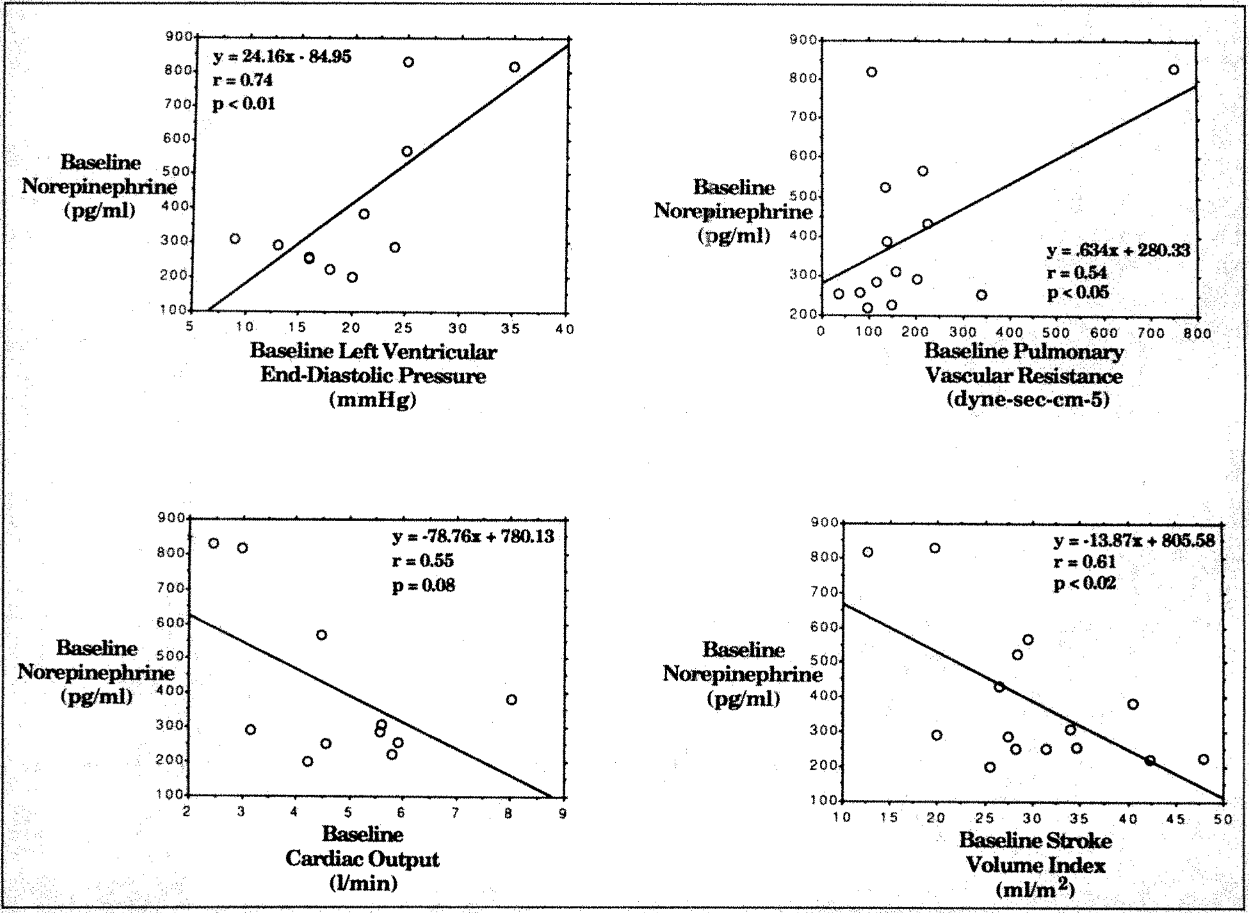

FIGURE 2. Baseline plasma norepinephrine did not correlate with left ventricular ejection fraction, end-systolic elastance or systemic vascular resistance. However, there were weak correlations with baseline left ventricular end-diastolic pressure ($r = 0.74$, $r^2 = 0.55$, $p < 0.01$), pulmonary vascular resistance ($r = 0.54$, $r^2 = 0.29$, $p < 0.05$), stroke volume index ($r = 0.61$, $r^2 = 0.37$, $p < 0.02$) and a trend with baseline cardiac output ($r = 0.55$, $r^2 = 0.3$, $p = 0.08$).

natively, the failure of plasma renin response to predict hemodynamic improvement may indicate that β-adrenergic blockers improve left ventricular function by mechanisms other than attenuation or blockade of neurohormonal activation.

The importance of reducing renin in the face of downstream angiotensin-converting enzyme inhibition has been questioned. However, recent evidence has suggested alternative enzyme systems that convert angiotensin I to angiotensin II.[21] Thus, even in the presence of an angiotensin-converting enzyme inhibitor, alternate pathways may permit the formation of angiotensin II and aldosterone, thus maintaining some adverse neurohormonal activation. "Upstream" blockade of renin release may provide more complete deactivation of this pathway. In addition, because not all patients will tolerate treatment with an angiotensin-converting enzyme inhibitor because of its hypotensive properties, the addition of a β-adrenergic blocker will significantly reduce activation of the renin-angiotensin system.

Effects on the sympathetic nervous system and plasma norepinephrine: Despite hemodynamic and functional improvement in these patients, no uniform reduction was seen in plasma norepinephrine. The reason for this unexpected finding is unclear, especially as others have shown reductions in plasma norepinephrine concentration and an increase in norepinephrine clearance as ventricular performance improves.[22,23] However, like these previous investigators, we found an inverse correlation between baseline plasma norepinephrine concentrations and cardiac output (Figure 2). Previous investigators have seen no change in plasma norepinephrine with the acute administration of pindolol in patients with heart failure.[17] However, lack of change in norepinephrine acutely is not surprising since the administration of β-adrenergic blockers may require several weeks to improve hemodynamics. Additionally, because plasma norepinephrine correlated weakly with left ventricular end-diastolic pressure, it may fluctuate with heart failure compensation and loading conditions of the heart and not directly represent inotropic and lusitropic function. Since the norepinephrine samples were obtained on the day of MIBG scintigraphy and not on the same day as cardiac catheterization, changes in ventricular compensation and filling pressures (which may simply reflect salt intake) may have altered plasma norepinephrine, even in the presence of improved contractility and relaxation by β blockers.

Unchanged MIBG uptake after β-blocker therapy suggests a lack of change in adrenergic norepinephrine uptake. The major defect in myocardial norepinephrine kinetics is decreased adrenergic uptake resulting in net myocardial depletion of norepinephrine.[6] We would expect MIBG uptake to increase if such an adrenergic defect was corrected with therapy. However, no such change was seen. Because plasma norepinephrine levels did not change, increased competitive uptake by norepinephrine could not account for a lack of change in MIBG counts.

In contrast to our study, others have documented a reduction in plasma norepinephrine levels after treatment with bucindolol.[15] The reason for the discrepancy between this previous study and ours remains unclear, but may be due to a difference in ventricular compensation at the time of study, especially during the initial study. In addition, the norepinephrine samples were obtained during cardiac catheterization in the study by Gilbert et al.[15] The anxiety and pain induced by catheterization may have played some role in their results. More extensive studies are needed to define the effect of β blockade on sympathetic activity.

Crossover neurohormonal antagonism: Previous animal studies have shown that angiotensin-converting enzyme inhibitors not only antagonize the renin-angiotensin system, but also may resensitize the cardiac β-adrenergic receptor-adenylate cyclase system[24] and may upregulate β receptors.[25] Angiotensin II is known to act at the presynaptic terminal to block neuronal uptake of norepinephrine[26] and enhance norepinephrine biosynthesis.[27] Thus, blockade of the renin-angiotensin system

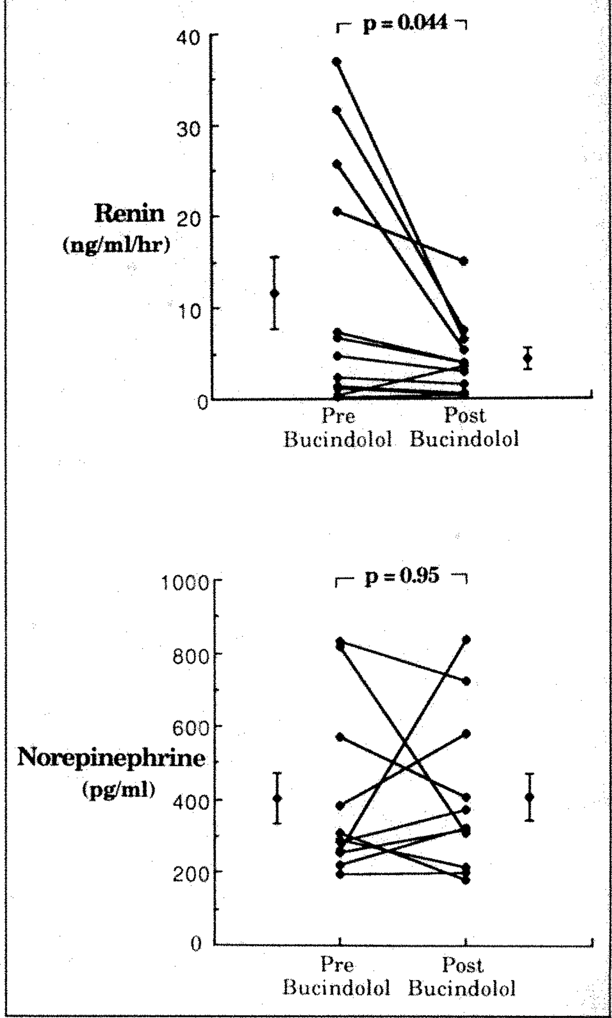

FIGURE 3. Bucindolol therapy reduced plasma renin activity *(top panel)*. However, there was no net effect on plasma norepinephrine *(bottom panel)*. A diversity of individual responses to bucindolol are evident, with some subjects having increased and others decreased norepinephrine levels after therapy. Values are expressed as mean ± standard error of the mean.

results in lower presynaptic norepinephrine and sympathetic activity.

Alternatively, β-adrenergic blockade not only provides blockade of the β-adrenergic receptors resulting in β upregulation and sensitization,[6] but also may inhibit the renin-angiotensin system as demonstrated by our data. Thus, these 2 neurohormonal systems may be antagonized by both β-adrenergic blockers and angiotensin-converting enzyme inhibitors. Moreover, our data suggest there may be a synergistic effect of these 2 agents working together that is superior to either agent alone. Since all but 1 patient were taking long-term converting enzyme inhibitors before entry into this study, and because most of these patients improved hemodynamically with the addition of bucindolol, one can infer additional benefit from β-adrenergic blockers. Since alternate pathways for renin-angiotensin activation have been suggested in the presence of converting enzyme inhibition,[21] the incremental improvement seen with the addition of a β antagonist may in part reflect more complete deactivation of the renin-angiotensin system, although a direct correlation was not observed.

Study limitations: Although the plasma catecholamine and plasma renin activities were, on the whole, not severely elevated, more significant changes may have been seen in patients with more neurohormonal activation at baseline. Furthermore, all samples were obtained from peripheral veins rather than from a mixed venous site. Thus, there may be some variation in absolute levels from what would have been seen had we obtained samples from the pulmonary artery. However, relative changes in renin and norepinephrine should not be influenced greatly by this. Furthermore, local receptor site concentrations of renin may not necessarily be reflected in the circulating plasma levels.[28]

Previous studies have shown a correlation between sympathetic nerve activity and plasma norepinephrine levels.[1] We therefore assumed that plasma norepinephrine levels delineated the status of the sympathetic nervous system. However, in the presence of β-adrenergic blockade and angiotensin II inhibition, this may be a poor reflection of the synaptic norepinephrine present, and almost certainly is nonrepresentative of the second messenger stimulation (i.e., effective norepinephrine stimulation).

Caution must be applied to interpretation of the data relating baseline norepinephrine to hemodynamic parameters (left ventricular end-diastolic pressure, stroke volume, pulmonary vascular resistance and cardiac output). These correlations are weak and the measurements were not made simultaneously. In addition, as multiple regressions were examined, a type II error could be present. However, previous studies have found correlations between pulmonary wedge pressure and sympathetic nerve traffic[1] and between baseline plasma norepinephrine levels and ejection fraction.[22] Thus, these observations are not inconsistent with previous data. Additionally, nonlinear correlations between stroke volume index and pulmonary vascular resistance and baseline norepinephrine levels have been reported.[17] However, we found these relations to fit a linear model better than a nonlinear model.

Since each patient was his own control, a formal control group consisting of patients who received only standard therapy was not included in this study. However, previous longitudinal studies have shown an increase in both plasma catecholamines and plasma renin activity over time.[11] Thus, an intervention that reduces plasma renin activity, especially in the face of chronic angiotensin-converting enzyme inhibition (which tends to raise plasma renin activity),[29] must be considered efficacious. Because no other intervention aside from β-adrenergic blockade was performed during the 3-month trial period, and because all other medications were unchanged for ≥2 months before study initiation, bucindolol must be considered an effective agent for reducing plasma renin activity. In addition, because supine plasma renin was obtained early in the morning (at approximately the same time of day) on the day of catheterization in each patient, circadian variability cannot account for changes in renin activity.

Increases in MIBG uptake could have been offset by decreases in adrenergic nerve numbers. Cardiomyopathic hearts have previously been shown to contain decreased numbers of neurons compared with normal hearts.[30] Thus, any further reduction in neuronal numbers might have offset any increase in MIBG uptake to result in a net lack of change in scintigraphic counts.

The results from our study cannot necessarily be extrapolated to all β blockers because they differ in their agonist and antagonist adrenergic properties.

Acknowledgment: We gratefully acknowledge Ronald Victor, MD, Michael R. Bristow, MD, and Brian Firth, MD, for their sensitive review of the manuscript. We express our appreciation to Donald Haagen, RCPT, Janie McCoulskey, CCRN, Willie Gary, Jenelle Durbin, RN, and Graciela Fields for their expert help during the performance of these studies.

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Effects of Percutaneous Transvenous Mitral Commissurotomy on Levels of Plasma Atrial Natriuretic Peptide During Exercise

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and Kunio Miyatake, MD

To clarify the factors that influenced the secretion of human atrial natriuretic peptide (ANP) during exercise, we studied the relations between the changes in ANP, transmitral pressure gradient, heart rate and blood pressure at exercise in 16 patients with mitral stenosis before and after percutaneous transvenous mitral commissurotomy (PTMC). Before PTMC, ANP levels increased from 107 ± 70 to 183 ± 96 pg/ml during exercise testing ($p < 0.01$), concomitant with the increment in mean transmitral pressure gradient, heart rate and systolic blood pressure. After PTMC, ANP levels also increased from 78 ± 43 to 117 ± 64 pg/ml, concomitant with the increment of those parameters. However, increments of ANP, mean transmitral pressure gradient and heart rate after PTMC were lower than those before PTMC. Because the most important factor influencing the secretion of ANP was unclear, the differences between these parameters were calculated at submaximal exercise before and after PTMC. There was a significant relation only between the change in ANP and mean transmitral pressure gradient ($r = 0.70$, $p < 0.01$). These results suggest that the most important factor influencing the secretion of ANP during exercise is the change in transmitral pressure gradient in patients with mitral stenosis.

(Am J Cardiol 1991;67:74–78)

Secretion of human atrial natriuretic peptide (ANP) was mainly influenced by hemodynamic changes, such as atrial pressure, atrial stretch or atrial pacing.[1,2] We reported that plasma ANP levels decreased immediately after percutaneous transvenous mitral commissurotomy (PTMC) concomitant with the rapid decrease in left atrial pressure in patients with mitral stenosis.[3] A good correlation was noted between the decrements of ANP and those of left atrial pressure. Many reports showed that exercise stress also stimulated the secretion of ANP concomitant with the increment of pulmonary artery wedge pressure, heart rate, systemic blood pressure, cardiac output, neurohumoral factors, and so forth.[4–8] Heart rate, systolic blood pressure and left atrial pressure might increase significantly during exercise stress testing in patients with mitral stenosis. However, the most important factor among these factors could not be clarified. Because there was no definite report about the dominant factor influencing the secretion of ANP during exercise, this study was conducted to determine the factor most affecting ANP secretion during exercise stress testing in patients with mitral stenosis.

METHODS

Patients: Sixteen patients (9 men and 7 women, age range 35 to 66 years [average 50]) with symptomatic mitral stenosis were studied. Each patient gave informed consent. Fifteen patients were in New York Heart Association functional class II, and 1 patient in class III before PTMC. Eight patients were in sinus rhythm, and 8 had atrial fibrillation during study. Medications, such as diuretics or digitalis, were not changed during this study.

Percutaneous transvenous mitral commissurotomy: All patients underwent PTMC by transseptal approach with the use of the Inoue balloon catheter in the same manner as previously described.[3,9,10] Right- and left-sided cardiac pressure and output were measured before and after PTMC. Left ventriculography was performed before and after PTMC in 15 patients. Severity of mitral regurgitation from left ventriculography was graded semiquantitatively from 1+ to 4+. Severity of mitral regurgitation that could not be evaluated by left ventriculography was decided by color flow imaging technique in the remaining 1 patient with renal dysfunction.

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TABLE I Clinical and Hemodynamic Data of Patients

No. of Pts.	Age (yr) & Sex	Rhythm	MVA (cm^2)		MPG (mm Hg)		MR Grade	
			Pre	Post	Pre	Post	Pre	Post
1	45F	SR	0.9	2.4	5	3	0	I
2	50M	SR	1.2	2.2	23	9	I	II
3	47F	SR	0.9	1.8	14	8	0	0
4	50F	SR	1.2	1.8	10	3	0	0
5	37F	SR	0.6	1.7	16	5	I	I
6	62M	SR	1.7	2.9	7	0	I	I
7	44F	SR	0.8	1.7	9	0	0	I
8	45M	SR	1.0	2.4	7	0	0	I
9	66M	AF	1.1	1.9	5	0	I	I
10	35M	AF	1.2	1.5	10	5	I	I
11	62F	AF	1.1	1.8	4	5	0	I
12	62M	AF	1.0	1.4	3	0	0	I
13	56M	AF	1.6	2.2	7	0	I	I
14	46M	AF	1.7	2.1	3	0	II	II
15	52F	AF	1.2	2.2	5	3	I	I
16	46M	AF	1.1	1.7	7	3	I	I
Mean	50		1.1	2.0*	8.4	2.8*		
± SD	8		0.3	0.4	5.3	3.0		

* $p < 0.01$, before versus after PTMC.

AF = atrial fibrillation; MPG = mean transmitral pressure gradient; MR = mitral regurgitation; MVA = mitral valve area; SR = sinus rhythm.

Exercise protocol: All patients performed supine bicycle exercise 2 days before and 5 days after PTMC. The work load was started at 0 or 25 W and increased in increments of 25 W at 3-minute intervals until the patient experienced fatigue or dyspnea before PTMC. The work load after PTMC was the same as that before PTMC. Heart rate and systemic blood pressure were measured at rest and at submaximal exercise.[10]

Measurement of transmitral pressure gradient and mitral valve area: All 16 patients were examined with Doppler echocardiography during exercise stress testing. Doppler echocardiographic data were obtained with an Aloka SSD-730 echo-Doppler system equipped with a 2.0-MHz mechanical transducer and were recorded on a strip-chart recorder at paper speed of 50 mm/s. All examinations were performed in the supine position. Mean transmitral pressure gradient was measured by computer analysis from the mitral inflow velocity profile with continuous-wave Doppler.[10] Mitral valve area was measured by planimetry from 2-dimensional echocardiography before and after PTMC. A mean of 5 to 10 measurements was used.

Blood sampling and hormone assays: Blood samples were obtained from an antecubital vein into the tube containing an ethylenediamine tetraacetic acid and aprotinin.[11] Blood samples were obtained at rest and at submaximal exercise. Plasma concentrations of ANP were determined by specific radioimmunoassay after extraction with octadecylsilane cartridges as previously described.[12]

Statistical analysis: Data were expressed as mean ± standard deviation. Comparisons of means for continuous variables were obtained using paired Student's *t* tests. Linear regression analysis was used to determine the correlations between the differences of ANP levels and those of hemodynamic parameters. A probability value <0.05 was considered significant.

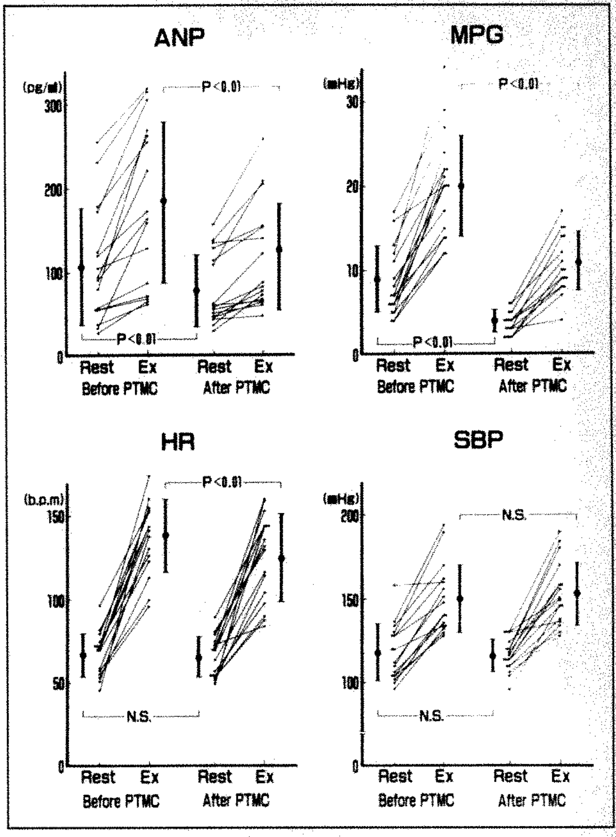

FIGURE 1. Plots of changes in plasma human atrial natriuretic polypeptide (ANP), mean transmitral pressure gradient (MPG), heart rate (HR) and systolic blood pressure (SBP) during exercise before and after percutaneous transvenous mitral commissurotomy (PTMC). N.S. = not significant.

RESULTS

Results of percutaneous transvenous mitral commissurotomy: The mitral valve area, evaluated by 2-dimensional echocardiography, increased from 1.1 ± 0.3 to 2.0 ± 0.4 cm^2 after PTMC in all patients ($p < 0.01$). Mean transmitral pressure gradient calculated by catheterization decreased from 8.4 ± 5.3 to 2.8 ± 3.0 mm Hg ($p < 0.01$). Mitral regurgitation increased in 6 patients after PTMC; however, no patient had severe mitral regurgitation greater than grade III after PTMC (Table I).

Changes in atrial natriuretic peptide levels: Plasma ANP levels increased from 107 ± 70 to 183 ± 96 pg/ml ($p < 0.01$) during exercise before PTMC and from 78 ± 43 to 117 ± 64 pg/ml ($p < 0.01$) during exercise after PTMC. There was a significant difference among the increments of ANP levels during exercise before (76 pg/ml) and after (39 pg/ml) PTMC ($p < 0.01$) (Table II, Figures 1 and 2).

Hemodynamic changes: Heart rate and systemic systolic blood pressure increased from 67 ± 13 beats/min and 118 ± 17 mm Hg to 138 ± 22 beats/min and 150 ± 20 mm Hg during exercise before PTMC, re-

TABLE II Hormonal and Hemodynamic Values During Exercise in Patients with Mitral Stenosis Before and After PTMC

	ANP (pg/ml)	MPG (mm Hg)	HR (beats/min)	SBP (mm Hg)
Before PTMC				
Rest	107 ± 70	9 ± 4	67 ± 13	118 ± 17
EX.	183 ± 96	20 ± 6	138 ± 22	150 ± 20
After PTMC				
Rest	78 ± 43*	4 ± 1*	66 ± 12	116 ± 10
EX.	117 ± 64*	11 ± 4*	125 ± 26*	150 ± 19

* $p < 0.01$, before versus after PTMC.

ANP = human atrial natriuretic polypeptide; EX. = submaximal exercise; HR = heart rate; MPG = mean transmitral pressure gradient; PTMC = percutaneous transvenous mitral commissurotomy; SBP = systolic blood pressure.

spectively ($p < 0.01$), and increased from 66 ± 12 beats/min and 116 ± 10 mm Hg to 125 ± 26 beats/min and 150 ± 19 mm Hg during exercise after PTMC, respectively ($p < 0.01$). There was a significant difference between the increments of heart rate during exercise before PTMC (70 ± 20 beats/min), and those after PTMC (59 ± 25 beats/min) ($p < 0.01$) (Table II, Figures 1 and 2). Mean transmitral pressure gradient also increased from 9 ± 4 to 20 ± 6 mm Hg during exercise before PTMC ($p < 0.01$), and increased from 4 ± 1 to 11 ± 4 mm Hg during exercise after PTMC ($p < 0.01$). There was a significant difference among the increments of mean transmitral pressure gradient during exercise before (11 ± 5 mm Hg) and after (7 ± 3 mm Hg) PTMC ($p < 0.01$) (Table II, Figures 1 and 2).

Regression analysis between the changes in plasma atrial natriuretic peptide and those in hemodynamic parameters: Before PTMC, there were correlations among the increments of plasma ANP levels and those of mean transmitral pressure gradient or systolic blood pressure, respectively ($r = 0.46$, $r = 0.61$) (Figure 3). After PTMC, there were also correlations between the increments of plasma ANP levels and those of mean transmitral pressure gradient or systolic blood pressure, respectively ($r = 0.54$, $r = 0.49$) (Figure 3). However,

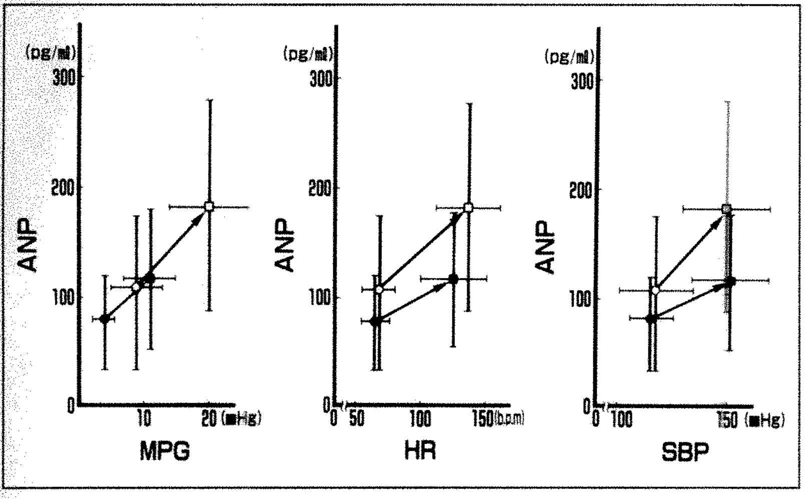

FIGURE 2. Changes in the relation between plasma human atrial natriuretic polypeptide (ANP) and mean transmitral pressure gradient (MPG) *(left panel),* heart rate (HR) *(center panel)* and systolic blood pressure (SBP) *(right panel)* during exercise before (*open circles,* rest; *open squares,* submaximum) and after *(closed circles,* rest; *closed squares,* submaximum*)* percutaneous transvenous mitral commissurotomy (PTMC).

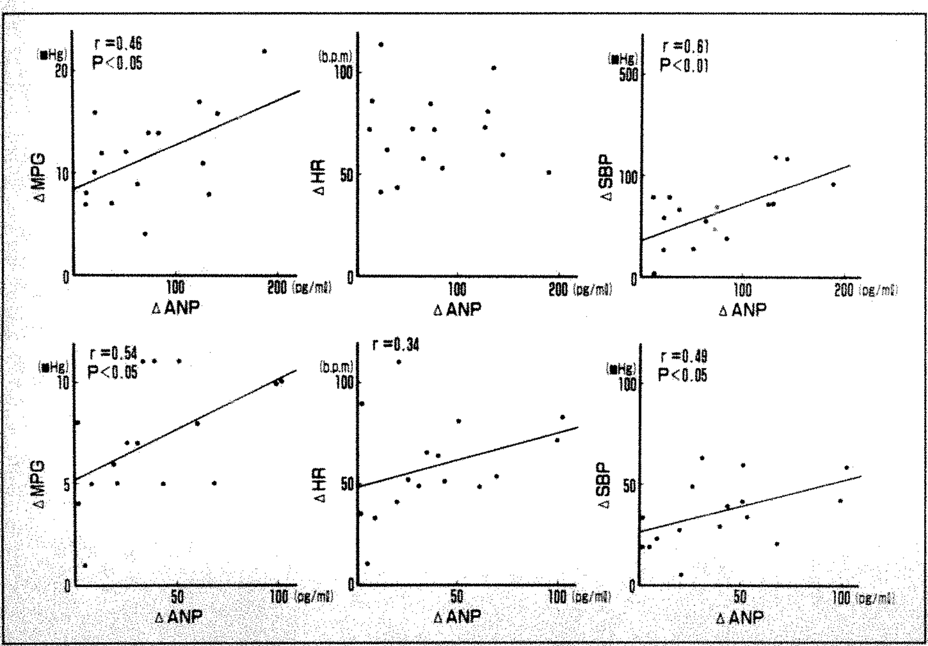

FIGURE 3. Plots of correlation between the changes in human atrial natriuretic polypeptide (ANP) and those in mean transmitral pressure gradient (MPG) *(left panel),* heart rate (HR) *(center panel)* and systemic blood pressure (SBP) *(right panel)* before *(upper panel)* and after *(lower panel)* percutaneous transvenous mitral commissurotomy (PTMC).

there were no significant correlations between the increments of plasma ANP levels and those of heart rate before and after PTMC.

Furthermore, to clarify the influence of secretion of ANP, we calculated differences between ANP levels at submaximal exercise before and after PTMC. We also calculated the differences in mean transmitral pressure gradient, heart rate and systolic blood pressure. The regression analysis of these differences were examined. There was a good correlation only between the difference in ANP and that of mean transmitral pressure gradient ($r = 0.70$, $p < 0.05$) (Figure 4). There were no significant correlations between the difference in ANP and that of other hemodynamic parameters.

DISCUSSION

Many reports have shown that exercise stress testing stimulates the secretion of ANP.[4-8] During exercise stress testing, several factors, such as heart rate, systolic blood pressure, atrial pressure, cardiac output and neurohumoral factors, changed. Therefore, it was difficult to determine the dominant factor influencing the secretion of ANP. Nishikimi et al[5] showed that ANP levels were significantly correlated with pulmonary wedge pressure during exercise stress testing; however, the relation between the changes in ANP and those in heart rate or systolic blood pressure were not examined.

Saito et al[4] showed that ANP secretion was exaggerated by the increments of systolic blood pressure in patients with essential hypertension. ANP secretion was correlated with systolic blood pressure, heart rate and plasma norepinephrine or epinephrine concentration in normotensive subjects. In their study, atrial pressure was not measured, and they suggested that a greater increase in atrial pressure resulting from an increase in systolic blood pressure was involved in the exaggerated secretion of ANP. Mckay et al[13] showed that during exercise, left ventricular end-diastolic pressure was minimally changed. Thus, transmitral pressure gradient appeared to reflect left atrial pressure during exercise. In our study, we measured transmitral pressure gradient estimated by Doppler echocardiography during exercise stress testing to evaluate left atrial pressure.

We could not evaluate right atrial pressure; however, the changes in right atrial pressure may be fewer than those in left atrial pressure in patients with mitral stenosis as shown in the previous report.[3] In patients with mitral stenosis, left atrial pressure may increase mainly by exercise stress testing.

An additional advantage of this study was that the relation between ANP levels and hemodynamic factors, such as transmitral pressure gradient, heart rate and systemic blood pressure were evaluated in the same patients undergoing PTMC, because ANP levels and the potential of the exercise-induced ANP secretion may vary in individual cases. In the present study, we showed that ANP levels increased concomitant with the increment of transmitral pressure gradient, heart rate and systolic blood pressure. Therefore, exercise stress testing only before PTMC could not reveal the major stimuli for secretion of ANP. After PTMC, ANP levels and transmitral pressure gradient at rest decreased despite unchanged heart rate and systolic blood pressure compared with factors before PTMC. These data were similar to our previous report.[3] After PTMC, once again ANP increased concomitant with the increments of transmitral pressure gradient, heart rate and systolic blood pressure during exercise stress testing. Then the differences between ANP, transmitral pressure gradient, heart rate and systemic blood pressure were examined during submaximal exercise before and after PTMC. A significant correlation was observed only between the differences in ANP and those of transmitral pressure gradient.

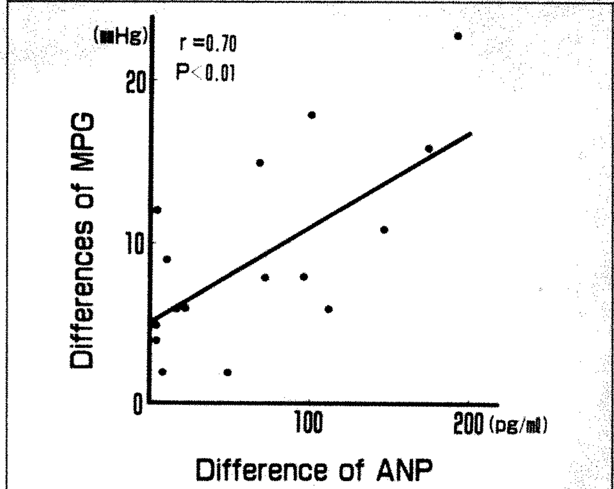

FIGURE 4. Plots of correlation between the difference in human atrial natriuretic polypeptide (ANP) and that in mean transmitral pressure gradient (MPG). The difference is ANP or MPG during submaximal exercise before PTMC minus that after PTMC.

In this study, the relation between ANP levels and other humoral factors was not evaluated. Saito et al[4] showed that plasma renin activity and plasma aldosterone concentration did not significantly increase during exercise, and there were no significant correlations between the changes in ANP and those in plasma renin activity or plasma aldosterone concentration.

In conclusion, these results suggest that the most important factor influencing the secretion of ANP during exercise may be the alteration of transmitral pressure gradient in patients with mitral stenosis. Measurements of ANP levels may be useful for managing patients with mitral stenosis.

Acknowledgment: We thank Deepak Natarajan, MD, Takenobu Kamada, MD, and Akira Kitabatake, MD, for their helpful comments on this work and Yukio Hirata, MD, for the presentation of the ANP antibody.

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Blood Rheology After Cardiac Valve Replacement with Mechanical Prostheses or Bioprostheses

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Arterial thromboembolism is a serious complication in patients after heart valve replacement. Abnormalities in blood rheology may contribute to this complication. Therefore, the aim of this study was to compare various determinants of blood rheology in patients with substitute heart valves with those in healthy controls; furthermore, differences between patients with mechanical valves and those with bioprostheses should be investigated. The hemorrheologic determinants—fibrinogen, plasma viscosity, red cell aggregation, hematocrit and platelet aggregation—were studied in 92 patients with mechanical bileaflet valves, in 28 patients with bioprostheses and in 29 control subjects; the time since valve replacement was ≥ 9 months. Fibrinogen, plasma viscosity, red cell and spontaneous platelet aggregation were found to be increased in all patients after heart valve replacement compared with normal subjects (fibrinogen: 348 ± 87 vs 267 ± 66 mg/dl, $p < 0.01$; plasma viscosity: 1.71 ± 0.1 vs 1.66 ± 0.1 mPas, $p < 0.05$; red cell aggregation: 9.9 ± 2 vs 7.8 ± 2 U, $p < 0.01$; platelet aggregation: 22 ± 15 vs 13 ± 13%, $p < 0.01$); among patients, fibrinogen, plasma viscosity and spontaneous platelet aggregation were higher in mechanical valves than in bioprostheses (fibrinogen: 359 ± 95 vs 314 ± 41 mg/dl, $p < 0.01$; plasma viscosity: 1.72 ± 0.1 vs 1.68 ± 0.1 mPas, $p < 0.1$; platelet aggregation: 23 ± 15 vs 16 ± 11%; $p < 0.05$), whereas no difference could be found for red cell aggregation (9.7 ± 2 vs 10.5 ± 2%, $p > 0.05$). Blood rheology factors were independent of the time of valve implantation, valve position, valve size and cardiac rhythm. Rheologic abnormalities in patients after heart valve replacement may contribute to thrombus formation at the site of the valve by further disturbing blood flow in regions of flow separation or stagnation, or both, created in the immediate vicinity of the prosthetic device.

(Am J Cardiol 1991;67:79–83)

Arterial thromboembolism is a serious complication in patients after heart valve replacement.[1–3] It is much more pronounced in patients with mechanical prostheses who therefore need a life-long anticoagulant therapy[3–6]; in patients with bioprostheses the thrombogenic risk is low so that anticoagulants are usually restricted to a short period.[2,3,7] A major role in the initiation of thrombus formation at the site of the valve has been ascribed to the activation of blood platelets.[8–12] However, therapy with platelet aggregation inhibitors alone has clearly failed to provide adequate protection from thromboembolism in patients with mechanical valves.[4,13] Other factors such as abnormalities in blood rheology may further contribute to this complication.

Therefore, the aim of this study was to evaluate the behavior of various determinants of blood rheology in patients after cardiac valve replacement compared with that in healthy controls. Furthermore, the difference between patients with mechanical valves and those with bioprostheses should be investigated.

METHODS

Patients: One hundred twenty patients (67 men, 53 women) after heart valve replacement were studied. Ninety-two patients (51 men, 41 women) had received mechanical prostheses (55 Duromedics-Edwards and 37 Carbomedics bileaflet valves; 50 aortic, 36 mitral, 6 double), whereas 28 patients (15 men, 13 women) had received bioprostheses (Sorin-Pericarbon [bovine pericard]; 24 aortic, 2 mitral, 2 double). The valve size (diameter) ranged from 21 to 33 mm in Duromedics-Edwards prostheses, from 19 to 29 mm in Carbomedics valves, and from 19 to 31 mm in Sorin-Pericarbon bioprostheses. The average time elapsed since operation was 27 months (range 10 to 36) in patients with mechanical valves, and 22 months (range 9 to 43) in patients with bioprostheses.

The patients were aged 26 to 80 years (mean ± standard deviation [SD] 58 ± 11 years in patients with mechanical valves, and mean ± SD 63 ± 8 years in patients with bioprostheses). All patients with mechanical valves were receiving oral anticoagulant therapy with phenprocoumon or acenocoumarol. Of the patients with biologic valves, only 2—patients with a history of thromboembolism—received oral anticoagulant therapy. All patients had normally functioning valve prostheses confirmed by echocardiography. Patients taking platelet aggregation inhibitors or hemorrheologically active drugs as well as smokers and patients with underlying diseases known to influence blood rheology (diabe-

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TABLE I Hemorrheologic Data in Patients After Cardiac Valve Replacement Compared with Healthy Controls

	Patients (n = 120)	Controls (n = 29)	p Value
Fibrinogen (mg/dl)	348 ± 87	267 ± 66	<0.01
Plasma viscosity (mPa/sec)	1.71 ± 0.1	1.66 ± 0.1	<0.05
Red cell aggregation (arbitrary units)	9.9 ± 2	7.8 ± 2	<0.01
Hematocrit (%)	44 ± 4	44 ± 4	NS
Platelet aggregation (%)			
Spontaneous	22 ± 15	13 ± 13	<0.01
ADP–induced	71 ± 14	66 ± 17	NS

Values are mean ± standard deviation.
ADP = adenosine diphosphate; NS = not significant.

tes mellitus, hyperlipidemia, arterial occlusive disease) were excluded from the study.

Blood samples were obtained without stasis from the antecubital vein for immediate determination of the following determinants of blood rheology: fibrinogen, plasma viscosity, red cell aggregation, hematocrit and platelet aggregation. Plasma fibrinogen was estimated with the method of Clauss.[14] Plasma viscosity was measured with a viscometer of the capillary type at 25°C (Coulter-Harkness viscometer, ethylene diaminetetraacetic acid plasma).[15] Red cell aggregation was determined using the MA1-Aggregometer, a photometric rheoscope (Myrenne, Roetgen, Federal Republic of Germany).[16] The measurements were obtained from heparinized blood (10 U/ml) adjusted to a standard hematocrit of 45% with autologous plasma at a low shear rate of 3/s. For determination of platelet aggregation, blood was anticoagulated with 1 part in 10 of 3.8% trisodium citrate and centrifuged to produce platelet-rich plasma; the platelet count was adjusted to 200×10^9/liter. Platelet aggregation (spontaneous and adenosine diphosphate (ADP)–induced [final concentration 5×10^{-7} mol/liter]) was measured with the PA2-Aggregometer (Myrenne[17]): Platelet-rich plasma was subjected to a constant shear rate of 40/s in a cone plate chamber. Microhematocrit levels were determined by centrifuging the sample at 15,000 g for 5 minutes.

Simultaneously, blood samples were obtained for routine hematologic and chemistry profiles, including the serum lactate dehydrogenase activity to estimate the degree of intravascular hemolysis.

Twenty-nine clinically healthy subjects (16 men, 13 women; mean age ± SD 59 ± 12 years), all nonsmokers without evidence of metabolic, neoplastic or inflammatory disease, were used as controls.

Results are expressed as mean ± SD. Intergroup comparisons were performed with the *t* test for unpaired data. Analysis of variance was applied to study hemorrheologic data in relation to valve position. Correlations were calculated according to Pearson.

RESULTS

All patients with substitute heart valves were compared with healthy controls (Table I); the differences between mechanical and biological valves are detailed in Table II.

TABLE II Hemorrheologic Data and Serum Lactate Dehydrogenase in Patients with Mechanical and Biologic Substitute Heart Valves

	Valves		
	Mechanical (n = 92)	Biologic (n = 28)	p Value
Fibrinogen (mg/dl)	359 ± 95	314 ± 41	<0.01
Plasma viscosity (mPa/sec)	1.72 ± 0.1	1.68 ± 0.1	<0.1
Red cell aggregation (arbitrary units)	9.7 ± 2	10.5 ± 2	NS
Hematocrit (%)	44 ± 4	43 ± 4	NS
Platelet aggregation (%)			
Spontaneous	23 ± 15	16 ± 11	<0.03
ADP–induced	71 ± 14	69 ± 14	NS
Serum lactate dehydrogenase (U/liter)	327 ± 131	275 ± 130	NS

Values are mean ± standard deviation.
ADP = adenosine diphosphate; NS = not significant.

Plasma fibrinogen was clearly elevated in patients with artificial valves compared with controls (Table I); this applied to each group of patients with valve replacement, those with mechanical devices ($p < 0.01$) and those with biologic valves ($p < 0.01$).

Plasma viscosity was increased in patients with substitute heart valves (Table I), in particular, in patients with mechanical valves ($p < 0.03$), whereas patients with bioprostheses were not different from controls ($p > 0.05$).

The increase in red cell aggregation in patients with valve replacement (Table I) applied to both patients with mechanical valves and patients with bioprostheses, respectively ($p < 0.01$ each).

Spontaneous platelet aggregation was increased in patients after heart valve replacement (Table I), particularly in patients with mechanical valves ($p < 0.01$), whereas no difference was seen between patients with bioprostheses and controls ($p > 0.05$).

No diffferences were seen with respect to hematocrit and ADP-induced platelet aggregation (Tables I and II).

Correlations of the hemorrheologic variables were found between fibrinogen level and red cell aggregation (Figure 1) and between fibrinogen and plasma viscosity (Figure 2).

Serum lactate dehydrogenase exceeded the upper limit of normal (240 U/ml) in both patient subgroups (Table II). Serum lactate dehydrogenase was inversely related to red cell aggregation (Figure 3). Furthermore, there was a positive correlation between serum lactate dehydrogenase and valve size ($r = 0.29$, $p < 0.01$). Valve size was inversely related to red cell aggregation ($r = -0.26$, $p < 0.01$).

Table III shows hemorrheologic variables and serum lactate dehydrogenase in detail with respect to valve position. Among patients with mechanical valves, a difference could be established for serum lactate dehydrogenase ($p < 0.05$) but not for the hemorrheologic variables (all $p > 0.05$). Numbers of patients with bioprostheses according to valve position were too small for statistical evaluation.

Cardiac rhythm (sinus rhythm or atrial fibrillation) as well as the time elapsed since operation were found to be unrelated to any of the variables studied (all $p > 0.05$).

Episodes of thromboembolism: In patients with mechanical valves, 1 episode of thromboembolism was manifested by stroke in a patient with aortic valve replacement, whereas anticoagulant therapy was well controlled (thrombotest values between 5 and 12%). Two patients with bioprostheses (aortic valve replacement) had transient ischemic attacks 2 and 4 months, respectively, after anticoagulant therapy had been discontinued.

DISCUSSION

Patients with cardiac valve replacement had increased plasma fibrinogen, plasma viscosity and red cell aggregation compared with those in normal subjects; fibrinogen and plasma viscosity were higher in patients with mechanical valves than in patients with bioprostheses.

With respect to fibrinogen, our results confirm previous observations[18] demonstrating elevated fibrinogen levels in patients with heart valve prostheses. However, the exact cause of hyperfibrinogenemia in these patients is not known. It cannot be attributed to the postoperative acute-phase reaction, as postoperative hyperfibrino-

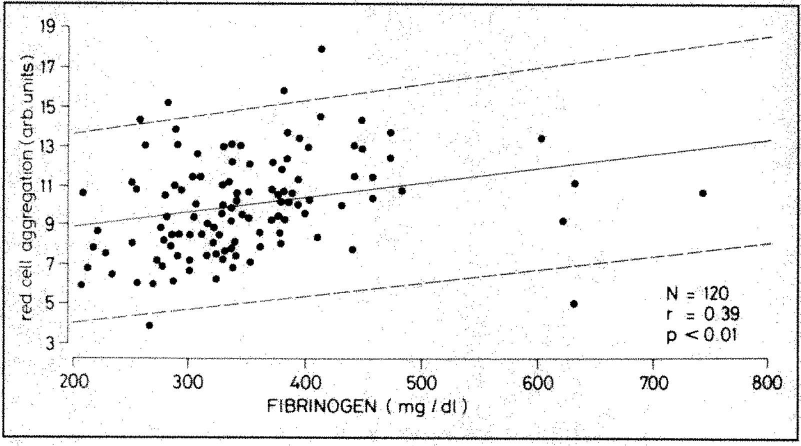

FIGURE 1. Correlation between fibrinogen and red cell aggregation in patients with cardiac valve replacement. arb. = arbitrary.

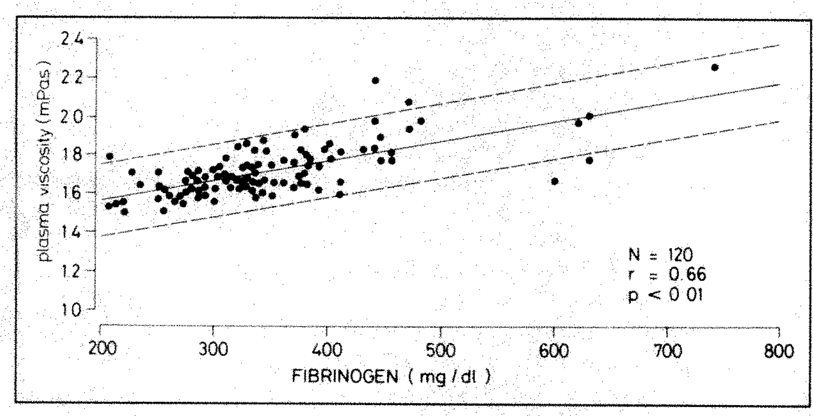

FIGURE 2. Correlation between fibrinogen and plasma viscosity in patients with cardiac valve replacement.

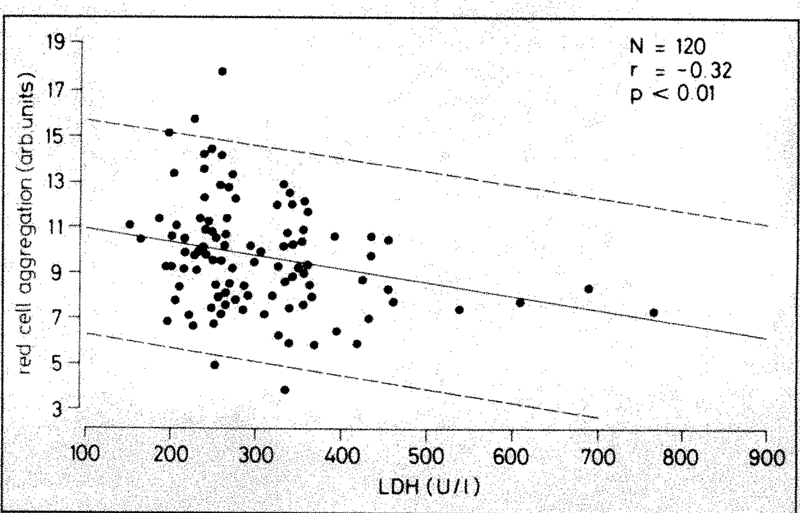

FIGURE 3. Inverse relation between serum lactate dehydrogenase (LDH) and red cell aggregation in patients with cardiac valve replacement. arb. = arbitrary.

TABLE III Hemorrheologic Data and Serum Lactate Dehydrogenase Related to Valve Position

	Aortic (n = 50)	Mitral (n = 36)	Double (n = 6)
Patients with Mechanical Prostheses			
Fibrinogen (mg/dl)	368 ± 113	347 ± 68	351 ± 67
Plasma viscosity (mPa/sec)	1.73 ± 0.1	1.71 ± 0.1	1.73 ± 0.2
Red cell aggregation (arbitrary units)	10.0 ± 2	9.5 ± 3	8.7 ± 2
Hematocrit (%)	44 ± 4	43 ± 4	43 ± 4
Platelet aggregation (%)			
Spontaneous	20 ± 13	25 ± 15	38 ± 28
ADP–induced	70 ± 15	70 ± 11	84 ± 11
Serum lactate dehydrogenase (U/liter)	288 ± 90	364 ± 162	406 ± 50
	Aortic (n = 24)	Mitral (n = 2)	Double (n = 2)
Patients with Bioprostheses			
Fibrinogen (mg/dl)	317 ± 37	264 ± 53	326 ± 72
Plasma viscosity (mPa/sec)	1.69 ± 0.1	1.71 ± 0.0	1.62 ± 0.0
Red cell aggregation (arbitrary units)	10.7 ± 2	9.5 ± 3	8.7 ± 0
Hematocrit (%)	43 ± 5	45 ± 2	44 ± 1
Platelet aggregation (%)			
Spontaneous	16 ± 12	12 ± 5	21 ± 9
ADP-induced	68 ± 14	69 ± 9	81 ± 10
Serum lactate dehydrogenase (U/liter)	274 ± 139	216 ± 44	345 ± 109

Values are expressed as mean ± standard.
Abbreviations as in Tables I and II.

genemia disappears within 14 days.[19] The same applies to anticoagulant treatment itself, which does not affect plasma fibrinogen.[20] Fibrinogen survival and turnover are relatively unchanged from normal in patients with heart valve replacement.[12,21] Thus, elevated fibrinogen levels may be part of an unspecific stress response to tissue injury, a so-called "hematologic stress syndrome," [22] which accompanies certain acute and chronic disorders and is characterized by increased hepatic synthesis of fibrinogen.

The increase in plasma fibrinogen results in 2 major rheologic consequences: an increase in plasma viscosity and an increase in red cell aggregation. Fibrinogen plays a major role in aggregation of red cells by acting as a bridging macromolecule between the cells.[23] The fact that red cell aggregation is the flow-limiting factor in areas of low shear may be of special importance in patients with valve prostheses: studies of hemodynamic performance have shown that artificial heart valves do not only create regions of elevated turbulent shear stresses large enough to cause damage to cellular blood elements, but also create regions of flow stagnation adjacent to the valve superstructure.[9-11] Increased red cell aggregation may seriously disturb blood flow in these regions of low shear and thus contribute to thrombus formation.

Our current findings with respect to spontaneous platelet aggregation, which was increased in patients with mechanical valves but not in patients with bioprostheses, support the view that mechanical valves are obviously more traumatic to blood platelets than bioprostheses.[12,21] Studies of ADP-induced platelet aggregability did not reveal marked deviations from the normal response; this finding is consistent with previous reports.[24]

The increase in serum lactate dehydrogenase activity in both patient subgroups indicates hemolytic properties of both valve types.[24] The degree of intravascular hemolysis—reflected by lactate dehydrogenase activity—was found to be inversely related to the extent of red cell aggregation: sublethal shear stresses at the site of the valve may damage red cell membranes and thus reduce their flexibility[25,26]; as red cell membranes have to deform for rouleaux formation to give maximal surface contact, a reduced flexibility may result in a reduction of erythrocyte aggregability. Even if this was the case in our patients, the absolute values of red cell aggregation remained increased because of the elevation in plasma fibrinogen.

We conclude that abnormalities in blood rheology present in patients after heart valve replacement were mainly related to the valve type because they were more pronounced with mechanical than with biologic valves. The fact that alterations in blood rheology co-exist with changes in platelet function may explain why therapy with platelet aggregation inhibitors alone without additional anticoagulant therapy failed to reduce the risk of arterial thromboembolism in patients with mechanical valves.[3]

Acknowledgment: I am indebted to Brigitta Wendelin and to Claudia Unger for excellent technical assistance.

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Hemodynamic Effects of Ketamine, Hypoxia and Hyperoxia in Children with Surgically Treated Congenital Heart Disease Residing ≥1,200 Meters Above Sea Level

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Little data are available on the hemodynamic effects of premedications and anesthetic agents on infants and children. Ketamine is the most frequently used anesthetic agent for cardiac catheterization procedures in pediatric patients with congenital heart disease. Previous reports both suggest and deny ketamine's pulmonary vasoreactive effects. Since the advent of sophisticated noninvasive equipment, one of the few indications for cardiac catheterization is to obtain accurate pressure data. If ketamine alters pulmonary vascular resistance, it would negate the primary reason for the procedure. Because the patient population studied herein resides ≥1,200 meters above sea level, concerns about pharmacologic effects on pulmonary vascular resistance are enhanced. Simultaneous pulmonary artery and aortic pressures, thermodilution cardiac outputs, and blood gases were measured in room air (16% oxygen) and with ketamine infusion in 14 patients at cardiac catheterization. Reaction to hypoxia identified 3 groups: normal, intermediate and hyperresponders. The normal responders had normal resistance ratios (0.11) in room air and had little resistance ratio response to hypoxia (+0.02), hyperoxia (−0.03) or ketamine (+0.01). The intermediate responders had a slightly higher but normal resistance ratio (0.20) in room air, and a moderate reaction to hypoxia (+0.13), hyperoxia (−0.08) and ketamine (+0.11). The hyperresponders had an elevated resistance ratio (0.42) in room air and a striking reaction to hypoxia (+0.65), hyperoxia (−0.17) and ketamine (+0.49).

Hypoxia and ketamine have a greater effect on resistance ratio than hypoxia alone in patients with reactive pulmonary vascular beds. Ketamine should not be used in children undergoing procedures to establish operability based on pulmonary vascular resistance or pulmonary vascular reactivity.

(Am J Cardiol 1991;67:84–87)

Little data are available on the hemodynamic effects of premedications[1-3] and anesthetic agents[4-7] on infants and children. Ketamine is the most frequently used anesthetic agent for cardiac catheterization procedures in pediatric patients with congenital heart disease.[8,9] Previous reports suggest that its use may be contraindicated in patients with pulmonary hypertension.[10-13] Two recent publications,[14,15] however, suggest that ketamine's effects on pulmonary vascular resistance are nil to trivial in infants and children with uncorrected or immediate postoperatively corrected congenital heart disease.

Since the advent of sophisticated noninvasive imaging methods of investigating congenital heart disease, one of the few remaining indications for cardiac catheterizations is to obtain accurate pressure data. Premedications or anesthetic agents that alter systemic or pulmonary vascular resistance during cardiac catheterization negate the primary reason for performing the procedure with its attendant risks. Furthermore, critical clinical decisions are often based on these hemodynamic data. Chronic residence at high altitudes appears to further increase pulmonary vascular reactivity to a variety of stimuli.[16-18] Because our patient population resides ≥1,200 meters above sea level, concerns about pharmacologic effects on pulmonary vascular resistance are greater than otherwise comparable pediatric cardiology centers at sea level.[19] This study examines the effects of ketamine, hypoxia and hyperoxia on the pulmonary and systemic vascular beds in children with surgically corrected congenital heart disease. All patients entered in the study had clinical or historical evidence of increased reactivity to hypoxia, plus ≥2 risk factors for increased pulmonary vascular reactivity.

METHODS

The study was approved by the human research committee of the University of Colorado School of Medicine. Informed consent was obtained from the parents of each child before the procedure. All children had had surgical correction of congenital heart disease ≥1 year prior. Each had a prior left-to-right shunt, with a pulmonary vascular resistance ≥50% of their systemic vascular resistance. In addition, ≥2 risk factors for a hyperreactive pulmonary vascular bed were required for entry into the study. These were: (1) residence at or above 2,500 meters; (2) preoperative pulmonary flow

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TABLE I Group Hemodynamic Data in Fourteen Patients in Room Air, Hypoxia, Hyperoxia and After Receiving Ketamine

Group	RA	16	100	K	RA	16	100	K	RA	16	100	K
	PAPX (mm Hg)				SAPX (mm Hg)				RR			
1	14.0	15.6	12.8	15.5	77.8	74.3	79.5	78.5	0.11	0.13	0.08	0.12
2	20.2	32.8	15.8	32.0	83.3	82.1	80.8	84.7	0.20	0.33	0.12	0.31
3	34.0	70.3	23.8	69.3	71.0	66.3	73.8	74.0	0.42	1.03	0.25	0.91
	CI (liters/min/m^2)				PVRI (U/m^2)				SVRI (U/m^2)			
1	4.6	4.7	3.6	4.4	1.8	2.1	2.0	2.2	17.0	16.0	26.7	18.0
2	4.8	4.9	3.9	4.4	3.5	5.5	2.6	5.8	17.6	16.5	21.3	19.0
3	5.1	5.0	4.0	5.0	5.4	12.7	4.2	12.6	13.0	12.3	16.8	13.9

CI = cardiac index; K = after ketamine infusion; PAPX = mean pulmonary artery pressure; PVRI = mean pulmonary vascular resistance index; RA = room air; RR = resistance ratio; SAPX = mean systemic arterial pressure; SVRI = systemic vascular resistance index; 16 = 16% ambient oxygen; 100 = 100% ambient oxygen.

greater than systemic flow; (3) Down syndrome; (4) clinical or laboratory evidence of baseline hypoventilation; (5) upper airway obstruction; (6) frequent respiratory infections (≥6/year); or (7) chronic lung disease. Fourteen children met criteria for the study. There were 8 boys and 6 girls ranging in age from 1.9 to 5.8 years (mean 3.6). One hour before the procedure, 2 mg/kg of meperidine and 1 mg/kg of hydroxyzine hydrochloride were administered intramuscularly. This combination of premedications has previously been shown to have little effect on pulmonary and systemic vascular hemodynamics.[2]

Percutaneous right-sided cardiac catheterizations and retrograde arterial procedures were performed in all subjects. Simultaneous pulmonary arterial phasic and mean pressures and central aortic phasic and mean pressures were recorded. Thermodilution cardiac outputs were done 3 times in the pulmonary artery. An average was calculated from 3 satisfactory curves. Simultaneous pulmonary arterial and central aortic samples were drawn, and partial pressure of oxygen (PO$_2$), partial pressure of carbon dioxide (PCO$_2$) and hydrogen ion concentration (pH) were determined. All variables were measured in room air, after 10 minutes of 16% inspired oxygen, and after 10 minutes of 100% inspired oxygen. After pressures and blood gases returned to baseline values, 1 mg/kg of intravenous ketamine was given and all measures repeated 3 to 5 minutes later. Right atrial and pulmonary arterial mean pressures were recorded with each set of data. Precapillary pulmonary and systemic vascular resistance indexes and ratios were calculated using the standard formula. No patient had residual shunts or significant obstructive lesions.

RESULTS

Patients were divided into 3 groups based on their response to hypoxia. Group averages for the salient hemodynamic data are listed in Table I. Group 1 consists of 4 patients with little response to hypoxia. These subjects are comparable to normal control subjects previously reported from our population[18] and are considered to be normal responders. Room air mean pulmonary artery pressure (14 mm Hg), pulmonary vascular resistance index (1.8 U/m^2) and resistance ratio (0.11) in group 1 were all normal for our altitude (Table I). Group 2 consists of 6 patients with an intermediate response to hypoxia. Room air mean pulmonary artery pressure (20.2), pulmonary vascular resistance index (3.5 U/m^2) and resistance ratio (0.20) in group 2 were in the high normal range (Table I). Group 3 consists of 4 patients with hyperresponsitivity to hypoxia. Room air mean pulmonary artery pressure (34 mm Hg), pulmonary vascular resistance index (5.4 U/m^2) and resistance ratio (0.42) in group 3 were elevated (Table I). The vascular reactivity of the 3 groups is shown in Figure 1. The ordinate axis, representing the resistance ratio from 0.0 to 1.2, reflects the simultaneous and comparative effects on the pulmonary and systemic circulations. The abscissa has 4 data intercepts: room air, 16% inspired oxygen, 100% inspired oxygen, and ketamine infusion. The 4 normal responders (group 1) had a room air resistance ratio of 0.11, which increased to 0.13 and 0.12 with hypoxia and ketamine, respectively, and decreased to 0.08 with 100% oxygen. The intermediate responders (group 2) had a room air resistance ratio of 0.20, which increased to 0.33 and 0.31 with hypoxia and ketamine, respectively, and decreased below baseline to 0.12 with hyperoxia. The hyperresponders (group 3) had a room air resistance ratio of 0.42, which increased to 1.03 and 0.91 with hypoxia and ketamine, respectively, and decreased below baseline to 0.25 with hyperoxia. Sheffe's test for multiple comparisons was performed for groups 2 and 3, and indicated statistically significant resistance ratio response to hypoxia and ketamine at the 0.05 probability level.

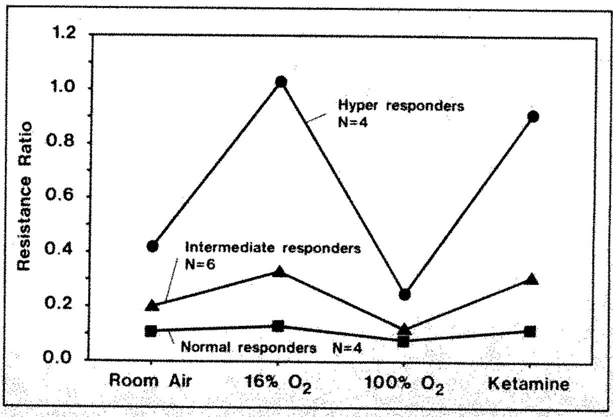

FIGURE 1. Changes in resistance ratio in response to hypoxia (16% oxygen), hyperoxia (100% oxygen) and ketamine infusion. O$_2$ = oxygen.

TABLE II Group Blood Gases in Fourteen Patients in Room Air, Hypoxia, Hyperoxia and After Receiving Ketamine

	pH				PCO_2				PO_2			
Group	RA	16	100	K	RA	16	100	K	RA	16	100	K
1	7.37	7.38	7.38	7.37	39	38	39	39	60	38	414	58
2	7.36	7.38	7.38	7.35	37	37	36	38	66	42	374	66
3	7.33	7.35	7.32	7.33	40	40	41	41	56	33	409	54

K = after ketamine infusion; PCO_2 = carbon dioxide partial pressure; pH = hydrogen ion concentration; PO_2 = oxygen partial pressure; RA = room air; 16 = 16% ambient oxygen; 100 = 100% ambient oxygen.

Cardiac index decreased approximately 1.0 liter/min/m^2 in all 3 groups with hyperoxia, decreased little with ketamine and was unresponsive to hypoxia (Table I). Group venous and arterial PO_2, PCO_2 and pH values are listed in Table II. Group 3 patients tended to have lower central PO_2 values in response to hypoxia, but in all other respects the values were comparable. Ketamine administration did not cause hypoventilation, hypoxia or acidosis. None of the patients experienced undesirable side effects.

DISCUSSION

Direct comparison of the hemodynamic responses of infants and children to ketamine, hypoxia and hyperoxia have not previously been reported. Previous studies looked at their independent effects in children with current or postoperative congenital heart disease.[18-20] The children in this study are a highly selected group with a greater than normal probability to be reactive to these stimuli. Consequently, the majority of patients demonstrated an increase in resistance ratio and pulmonary vascular resistance to both hypoxia and ketamine.

Down syndrome: The association of Down syndrome with pulmonary hypertension or pulmonary vascular reactivity is controversial and difficult to study.[21-25] Morray et al[14] concluded that Down syndrome was not a contributor to pulmonary vascular hyperreactivity, but 1 of their 2 hyperresponders was affected. Three of 4 of our group 3 patients had Down syndrome, whereas none of group 1 or 2 patients did. Conclusions regarding independent Down syndrome pulmonary vasoreactive propensity are difficult to reach because additional risk factors, such as upper airway obstruction and frequent respiratory infections, may be present in affected individuals.

Hyperoxia: Most of the published reports concerning pulmonary vascular reactivity and operability of children with congenital heart disease focus on the response to acute hyperoxia.[26,27] There are multiple problems with this method: First, shunt calculation becomes less accurate, making pulmonary vascular reactivity a rough estimate at best. Second, cardiac output decreased 22% in our study and 21% in the study reported by Beekman et al[27] with acute hyperoxia. Unless cardiac output is accurately measured (and not estimated), pulmonary vascular reactivity will be falsely elevated. Third, systemic vascular resistance increased 57 and 30% in our patients and in those reported by Beekman et al,[27] respectively. It is clear that, with complex interactions among these 3 variables, accurate calculation of pulmonary vascular reactivity in routine cardiac catheterizations is difficult.

Hypoxia: Hypoxia has been studied less often than hyperoxia as a pulmonary vascular stimulant.[26] Waldman et al[28] reported an excellent study of 22 children at sea level before and after correction of congenital heart disease, noting 2 of 22 to be hyperreactors. In some respects, they were comparable to our group 3 children, as they rapidly developed suprasystemic pulmonary pressure and profound intrapulmonary shunting with low aortic PO_2 values. Figure 1 shows that hypoxia is a more potent pulmonary vascular stimulus than hyperoxia. In our study, hypoxia caused increases in resistance ratio of 17, 76 and 123% above room air baseline values in groups 1, 2 and 3, respectively, whereas hyperoxia caused decreases of 11, 20 and 32%, respectively. Hypoxia is a more frequently encountered "physiologic" stimulus than hyperoxia. Visits to or residence at high altitude, airplane travel, respiratory infection, chronic lung disease and upper airway obstruction are all hypoxic events experienced by children with congenital heart disease.

Ketamine: Ketamine is a safe and commonly used anesthetic agent in pediatric cardiac catheterizations.[8,9] If, however, it causes significant pulmonary vasoconstriction[10-13] in hyperresponders, misleading hemodynamic data and high-risk procedures may be the consequence. Two recent studies suggest that ketamine causes insignificant pulmonary vascular reactivity changes[14,15] in children with congenital heart disease. Morray et al[14] evaluated 20 children with uncorrected defects who received ketamine at cardiac catheterization. Close perusal of their data, however, reveals that 5 of 20 patients had a pulmonary artery pressure of ≥25 mm Hg and that their pulmonary artery pressures increased with ketamine administration while they were breathing room air. These patients are similar to our group 2 intermediate responders. Hickey et al[15] evaluated 14 intubated children the day after corrective surgery for congenital heart disease. Their conclusion was that ketamine had no pulmonary vasoconstrictive effect and that previous studies actually reflected pulmonary vascular reactivity responses to hypoventilation. These investigators, however, were giving forced inspiratory oxygen of 0.3 to 0.4 during ketamine administration, which may have offset and masked the ketamine pulmonary vasoconstrictive effect. Berman et al[20] recently showed that ketamine caused significant increases in pulmonary vascular reactivity, heart rate and oxygen consumption in subjects with baseline elevation of pulmonary vascular resistance.

Ketamine and hypoxia caused significant and, in some cases, dramatic increases in resistance ratio in our patients. Hypoxia was a more potent pulmonary vasoactive stimulus than hyperoxia. Although comparable patients may be found less frequently at sea level, it would seem reasonable to identify patients with multiple risk factors for pulmonary vascular hyperreactivity, and to use agents other than ketamine at cardiac catheterization. Specifically, ketamine should be used with caution in children undergoing procedures to establish operability based on pulmonary artery pressure or pulmonary vasoreactivity.

Acknowledgment: The secretarial and editorial assistance of Debra S. Osborne is greatly appreciated.

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Comparison of Exercise Stress Testing with Ambulatory Electrocardiographic Monitoring in the Detection of Myocardial Ischemia After Unstable Angina Pectoris

Ian Wilcox, BMedSci, MB, S. Ben Freedman, MB, PhD, Jianan Li, MMed, Phillip J. Harris, MB, DPhil, and David T. Kelly, MB

Exercise testing, considered to be contraindicated in unstable angina,[1] has recently been reported to be safe in patients whose symptoms have stabilized on medical therapy,[2] although this is not uniformly accepted.[3] Abnormal exercise responses in patients with recently stabilized unstable angina are associated with more extensive coronary artery disease[4] and a worse prognosis.[3,5] Detection of ischemia on continuous electrocardiographic (ECG) recordings performed early during hospitalization for unstable angina has been shown to indicate an adverse prognosis.[6–10] Preliminary data suggest that continuing silent myocardial ischemia detected by ambulatory ECG monitoring at the time of hospital discharge also denotes an adverse prognosis,[11] but there are no studies comparing exercise testing with ambulatory monitoring. In this study we compared exercise testing and ambulatory monitoring for the detection of myocardial ischemia in 32 medically stabilized patients at discharge after hospitalization for unstable angina pectoris.

Additional criteria were age <75 years, physical ability to exercise, and resting electrocardiogram that was interpretable for ischemia (absence of resting ST depression >1 mm, left ventricular hypertrophy or left bundle branch block). In a 10-month period, 33 patients were selected; 1 was later excluded because of an inadequate (<9 hours) ambulatory recording. The 32 patients comprised 22 men and 10 women, mean age 59 ± 9 years. Coronary angiograms, although not required for diagnosis, were available in 21 of 32 (66%) patients and revealed significant coronary artery disease ($\geq 50\%$ luminal diameter reduction) in 20 of 21 (95%).

All patients underwent simultaneous exercise testing and ambulatory monitoring within 2 days of hospital discharge. Medical therapy was continued during both tests and included β blockers in 15 (47%), calcium antagonists in 18 (56%) and nitrates in 25 (78%). Exercise testing was performed on a treadmill with a Naughton protocol and 12-lead ECG recording. The end point was the onset of angina or limiting nonanginal symptoms. Tests were terminated prematurely if patients developed ≥ 0.3 mV ST depression or an abnormal blood pressure response. A positive exercise electrocardiogram was defined as ≥ 0.1 mV horizontal or downsloping ST depression measured 80 ms after the J point, or ≥ 0.1 mV ST elevation. Ambulatory ECG monitoring was performed using a single-channel, solid-state, real-time ECG monitor (QMED Monitor One), which we have previously validated.[12] The monitoring lead was bipolar lead CS5. An ischemic episode was defined as ≥ 0.1 mV horizontal or downsloping ST depression or ≥ 0.1 mV ST elevation measured 60 ms after the J point and lasting >40 seconds. Postural ST-segment changes were excluded by recording ECG strips in the supine, right and left lateral decubitus, sitting and standing positions. Ambulatory monitoring, begun before the exercise test, continued for 35 ± 7 hours (mean ± standard deviation), the approximate lifespan of the batteries. Ischemic episodes that occurred during the simultaneously recorded exercise test were not included as ambulatory ischemic episodes. All ischemic episodes detected by the device were verified by inspection of the sample ECG trace stored during the episode.

Comparisons of continuous variables between groups were performed using unpaired t *tests. Differences in proportions were compared using contingency tables and the conditional binomial exact test. A p value <0.05 was considered significant. Values are given as mean ± standard deviation.*

Patients exercised for 10.8 ± 5 minutes, reaching 72 ± 13% of their predicted maximum heart rate at a work load of 5.8 ± 2.6 METs. Angina limited the test in 13 (41%). The exercise electrocardiogram was positive in 16 (50%) patients, 8 with and 8 without angina, whereas 4 patients had angina without ECG changes. Most patients (14 of 16, 88%) with a positive electrocardiogram had ≥ 0.1 mV ST-segment depression in lead V_5 and in 11 of 16 (69%) patients this lead was the site of maximal ST depression. Patients with a positive exercise electrocardiogram had an exercise capacity (5.4 ± 2.7 METs) similar to patients with a negative exercise electrocardiogram (6.1 ± 2.6 METs, difference not significant) and also attained a similar peak heart rate (75 ± 14% of predicted maximum vs 69 ± 14%, difference not significant).

Eight patients (25%) had a total of 49 ischemic episodes (mean 6 per patient, range 1 to 30) during 1,151 hours of ambulatory monitoring. All episodes were associated with ST depression, none with ST elevation. The majority of episodes (41 of 49, 84%) were silent, and 7 of 8 patients had silent ischemia, including 3 with exclusively silent ischemia. One patient had symptomatic ischemia only. In 5 additional patients, the only episode of ischemia occurred during the simultaneous exercise test.

From the Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Missendon Road, Camperdown, NSW 2050 Australia. Manuscript received May 15, 1990; revised manuscript received and accepted August 21, 1990. Dr. Wilcox was supported by a Postgraduate Medical Research Scholarship from the National Heart Foundation of Australia, and Dr. Li by an Overseas Scholarship from the World Health Organization. The study was supported in part by a grant-in-aid from the National Health and Medical Research Council of Australia, and by a grant from QMED, Inc., Clark, New Jersey.

There was no relationship between angiographic severity of coronary artery disease and ischemic episodes during ambulatory monitoring: of 21 patients with angiographically defined coronary artery disease, the mean number of diseased vessels was similar in the 4 with and in the 17 without ambulatory ischemia (1.3 ± 0.7 vs 2.0 ± 0.8, difference not significant).

There was a close relationship between ST depression during exercise and ischemic episodes during ambulatory monitoring. Seven of 16 patients (44%) with a positive exercise electrocardiogram had ambulatory ischemia, compared to only 1 of 16 (6%) with a negative exercise electrocardiogram ($p = 0.02$). Of the 16 patients with a positive exercise electrocardiogram, 3 (19%) had exclusively silent ambulatory ischemia. Thus, most patients (7 of 8, 88%) with ambulatory ischemia, including those with exclusively silent ambulatory ischemia (3 of 3, 100%), had a positive exercise electrocardiogram.

The degree of ST depression during exercise was also related to the occurrence of ambulatory ischemia (Figure 1), with the proportion of patients showing ambulatory ischemia increasing as maximal ST depression during exercise increased. Three of 5 patients (60%) with ≥ 0.2 mV ST depression had ambulatory ischemia, compared with 4 of 11 (36%) with ST depression between 0.1 to 0.19 mV and 1 of 16 (6%) with <0.1 mV ST depression ($p = 0.03$, Figure 1).

Angina during the exercise test did not predict ischemic episodes during ambulatory monitoring: 5 of 13 patients (38%) with angina during the exercise test had ambulatory ischemia compared with 3 of 19 (16%) without angina (difference not significant). No other exercise test variables, including exercise duration, work load and peak heart rate × pressure product, identified patients likely to have ambulatory ischemia.

Of the 16 patients with a positive exercise electrocardiogram, 12 had ST depression on the ambulatory recording during the exercise test, and ambulatory ischemia occurred in 7 of these 12 (58%). In the 4 patients with positive exercise electrocardiograms but no ST depression on the ambulatory recording during the exercise test, the exercise electrocardiogram was negative in lead V_5 (2 patients), or only mildly positive (<0.15 mV ST depression). Thus, the failure to demonstrate ST changes on the ambulatory recorder during exercise in the latter 4 patients appeared to be due to either the inherent limitation of single-lead ST monitoring, or less severe ischemia of shorter duration, because the device's algorithm required >40 seconds of ST depression >0.1 mV to define an ischemic episode. Minor differences in the position of the V_5 electrode, necessitated by simultaneous recording through 2 separate electrodes, may also have played a role.

In the present study, exercise stress testing detected myocardial ischemia after unstable angina in a substantially greater proportion of patients (50%) than did ambulatory monitoring (25%). The lower yield of ischemic episodes during ambulatory monitoring was only partly due to the use of a single-lead system, as 42% of patients with ST depression detected by the ambulatory recorder during the exercise test did not have ambulatory ischemia during everyday life. Adding a second ambulatory monitoring lead would probably have increased the incidence slightly. The main reason for the lower incidence of ambulatory ischemia was its relative rarity in patients with a negative exercise test, as has previously been found in patients with stable angina.[13]

Most patients with ischemic episodes during ambulatory monitoring had a positive exercise electrocardiogram. Adding ambulatory monitoring to exercise testing identified only an additional 6% of patients with ischemic ST-segment changes. The relatively small improvement in the detection of myocardial ischemia after unstable angina obtained by combining exercise testing with ambulatory monitoring is similar to that reported previously in patients with stable angina.[13] Nevertheless, ambulatory recordings revealed frequent episodes of ischemia (mostly silent) during everyday life in 44% of the patients with a positive exercise test, and 19% of the patients had exclusively silent ambulatory ischemia. This information may have important therapeutic implications, and may also provide independent prognostic information similar to that reported in patients with stable angina[14] and after myocardial infarction.[15]

In patients with recent unstable angina who have become asymptomatic on medical therapy, exercise testing identifies those with myocardial ischemia better than does ambulatory ECG monitoring. Patients with positive exercise electrocardiograms are likely to have ischemia during ambulatory monitoring, especially if the exercise test is strongly positive (≥ 0.2 mV ST depression). Ischemic episodes are mostly asymptomatic and therefore not appreciated by the patient or physician and may have important prognostic implications. Thus, ambulatory ECG recordings add important additional information when the exercise test is positive, but appear to be of little value in patients with a negative exercise electrocardiogram.

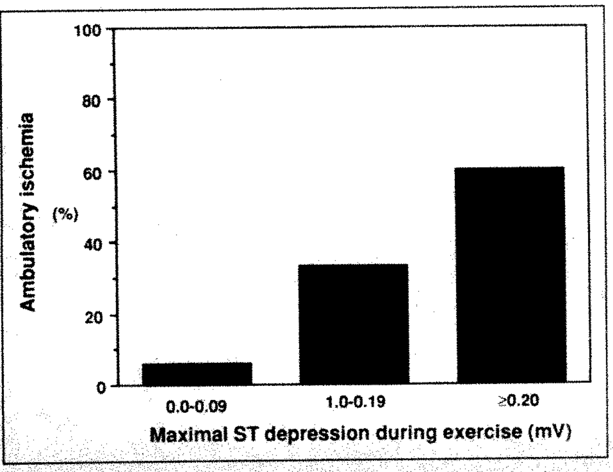

FIGURE 1. Relation between maximal ST depression during exercise testing and the incidence of ambulatory ischemia ($p = 0.03$).

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Circadian Variation in Pain Onset in Unstable Angina Pectoris

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Unstable angina pectoris has been recognized as an intermediate syndrome between stable angina pectoris and overt acute myocardial infarction with the same underlying pathophysiologic thrombotic mechanisms as the latter. We investigated the circadian distribution of pain onset in patients with unstable angina pectoris and compared it with that of acute myocardial infarction and sudden coronary death.

During the duration of the Secondary Prevention Reinfarction Israeli Nifedipine Reinfarction Trial-2 (SPRINT-2),[1] designed to investigate the early administration of nifedipine in acute myocardial infarction, there were 5,037 admissions to 14 coronary care units in Israel. Among these, 2,755 patients with acute coronary pain were admitted with suspected myocardial infarction. For this trial, 1,358 patients were randomized to oral nifedipine or placebo.

We reviewed the clinical charts of 377 patients among randomized as well as nonrandomized patients, with the diagnosis of unstable angina pectoris based on a typical anginal pain occurring at rest, and lasting <30 minutes, accompanied by reversible ST-segment or T-wave changes, or both, and without significant increase in serum cardiac enzymes. Demographic and clinical data, history and hospital course were prospectively recorded. Seventy-six patients were excluded from analysis because of insufficient data with respect to time of pain onset. The remaining 301 patients in the study were aged 36 to 79 years (mean 63): 236 (78%) were men and 147 patients (49%) had a myocardial infarction before the unstable anginal episode.

To evaluate the circadian distribution of pain onset, patients were grouped according to the time of onset of

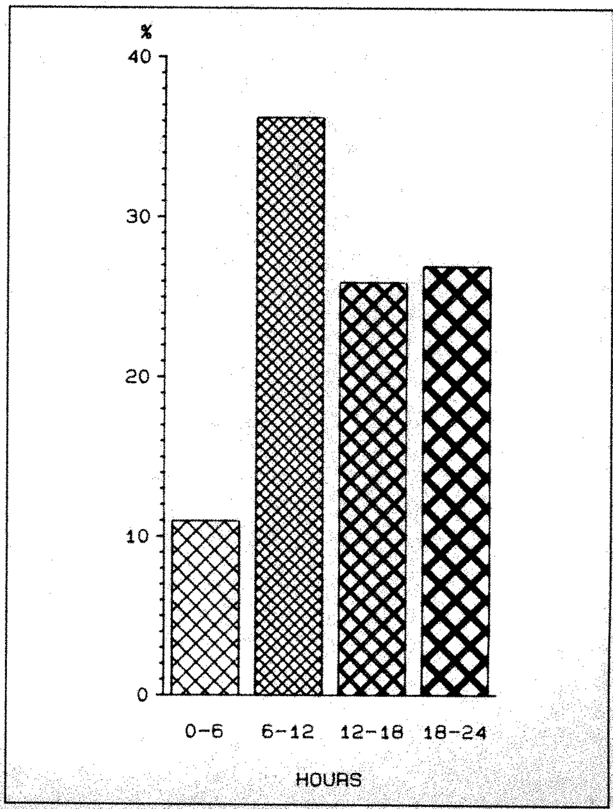

FIGURE 1. Time of onset of pain in patients with unstable angina at 6-hour intervals.

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*See Appendix.

TABLE I Circadian Variation of Pain Onset in Unstable Angina Pectoris According to Gender, Age and History

	No. of Pts.	Midnight–6 A.M.		6 A.M.–Noon		Noon–6 P.M.		6 P.M.–Midnight		p Value*
		No.	%	No.	%	No.	%	No.	%	
Men	236	23	10	86	37	66	28	61	26	<0.001
Women	65	10	15	23	35	12	18	20	31	0.07
Age (yrs)										
≤59	119	7	6	49	47	30	26	33	27	<0.001
60–69	100	13	12	36	36	23	24	28	29	0.01
≥70	82	13	16	24	28	25	31	20	25	0.20
History										
Myocardial infarction										
+	147	19	13	44	30	40	27	44	30	
0	154	14	9	65	42	38	25	37	24	
Angina pectoris										
+	188	20	11	64	34	51	27	53	28	
0	113	13	12	45	40	27	24	28	25	
Systemic hypertension										
+	122	7	6	48	39	35	29	32	26	
0	179	26	15	61	34	43	24	49	27	
Cigarette smokers										
+	184	16	9	67	36	51	28	50	27	
0	117	17	15	42	36	27	23	31	27	
All patients	301	33	11	109	36	78	26	81	27	<0.001

* Probability of deviation from identical distribution in 6-hour groups merely through sampling variation.
+ = present; 0 = absent.

symptoms in 3- and 6-hour intervals. The peak incidence of pain onset occurred between 6 A.M. and noon (p <0.001) (Figure 1). The circadian distribution of pain onset was analyzed also by gender, age groups and previous medical history. The morning peak prevalence was present in each of the analyzed subgroups (Table I). Although small subgroups of patients, such as women or those aged >70 years, do not achieve a nominal statistical significance, the overall picture of morning peak predominance is similar. Patient characteristics according to the time of onset of pain are provided in Table II. The group of patients in the morning peak of pain onset (6 A.M. to noon) were slightly younger and included more patients with a first myocardial infarction and higher rate of smokers, and specifically more patients with known hypertension than patients in whom pain onset starts between midnight and 6 A.M. The overall deviation in distribution of all "history" variables, between the four 6-hour spans, from equality, did not reach statistical significance below 0.10 in any of these variables. Mean blood pressure and heart rate on admission to the coronary care unit increased from 129/82 and 79 beats/min in patients with pain starting before 6 A.M. to 150/91 mm Hg (p <0.05) and 81 beats/min (difference not significant) in patients in whom the pain started after noon. In addition, morning peak incidence of pain onset in unstable angina pectoris was not influenced by the season of the year or by the day of the week (data not shown).

TABLE II Patient Characteristics According to Time of Pain Onset in Unstable Angina Pectoris

	Midnight–6 A.M.		6 A.M.–Noon		Noon–6 P.M.		6 P.M.–Midnight	
	No.	%	No.	%	No.	%	No.	%
Men	23	70	86	79	66	85	61	75
Mean age (years)	65		61		62		62	
Blood pressure on admission (mm Hg)	129/82*		133/80		150/91		154/90	
Heart rate on admission (beats/min)	79		78		81		83	
History								
Myocardial infarction	19	58	44	40	40	51	44	54
Angina pectoris	20	61	64	59	51	65	53	65
Systemic hypertension	7	21	48	44	35	45	32	40
Diabetes mellitus	6	18	20	18	18	23	18	22
Cigarette smokers	16	48	67	61	51	65	50	62

* Levels varied significantly (p <0.05) among the four 6-hour time periods.

This study clearly demonstrates a statistically significant variation in the circadian distribution of pain onset in unstable angina pectoris. The maximum incidence of pain onset in the morning hours, with a decline in the afternoon, is in complete accordance with the circadian pattern distribution observed in sudden coronary death, acute myocardial infarction, silent ambulatory ischemia, pulmonary emboli and stroke.[2-6]

The results of this study provide support for the hypothesis that unstable angina pectoris and acute myocardial infarction have a common pathophysiologic basis. In both cases the morning peak incidence of pain may represent a combination of hemostatic factors[7] (decrease in fibrinolytic activity and antithrombin III level and an increase in platelet aggregability) and an increase in sympathetic tone that occurs on awakening and provokes a significant increase in coronary tone, myocardial contractility, blood pressure and heart rate,[8] all of which may also lead to plaque rupture or fissure that forms the substrate for thrombus formation. In addition, the morning increase in plasma catecholamines, by further augmenting the direct effects of the sympathetic nervous system, expands the oxygen demand of the myocardium. All these factors may be the basis for the precipitation of myocardial ischemia in patients with advanced coronary disease.[9]

Better understanding of the endogenous biologic functions and the morning physiologic changes of the clinical manifestations of ischemic heart disease may lead to improved control of the precipitating factors and guide toward more effective therapeutic interventions.

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APPENDIX
SPRINT STUDY GROUP

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Decrease of Right and Left Atrial Sizes After Direct-Current Electrical Cardioversion in Chronic Atrial Fibrillation

Isabelle C. Van Gelder, MD, Harry J. Crijns, MD, Wiek H. Van Gilst, PhD, Hans P. M. Hamer, MD, and Kong I. Lie, MD

In chronic atrial fibrillation (AF), atrial enlargement is considered both a cause and a consequence of the arrhythmia.[1-4] It is not well known whether restoration and long-term maintenance of sinus rhythm indeed causes a reversal of the process of atrial enlargement.[5] In addition, the influence of the type of underlying heart disease on this process has not been studied. Therefore, we assessed whether atrial sizes decrease after electrical cardioversion in patients with chronic AF using 2-dimensional echocardiography.

Between January 1988 and January 1989, 120 patients with chronic AF were cardioverted to sinus rhythm. Sixty patients remained in sinus rhythm for ≥6 months. In 49 of these patients, fully evaluable echocardiographic recordings could be obtained. These 49 patients were the subject of the present study. Chronic AF was defined as documented AF with a duration of >24 hours without intercurrent sinus rhythm. The type of underlying heart disease was determined from the patient's history, physical examination, 12-lead electrocardiogram, chest x-ray, 2-dimensional echocardiogram, bicycle exercise test and, if available, coronary angiogram. In all patients, hyperthyroidism was excluded using standard tests. "Lone" AF was diagnosed only in the absence of any demonstrable underlying heart disease.[6] *Mitral valve disease was of rheumatic ($n = 9$), congenital ($n = 1$) or ischemic ($n = 1$) origin, and 10 of the patients in this group had mitral stenosis. Twenty-five patients with other underlying heart diseases were included in the nonmitral heart disease group. Coronary artery disease was present in 11 patients, hypertensive*

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heart disease in 7 patients, aortic valve disease in 4 patients, corrected hyperthyroidism in 1 patient and mitral valve prolapse without mitral regurgitation in 1 patient. One patient had undergone cardiac surgery because of a myxoma. The other 13 patients formed the group with lone AF. After the cardioversion, antiarrhythmic prophylactic drug treatment was instituted in 42 patients, depending on ongoing antiarrhythmic drug studies. These drugs were continued during follow-up. All other drug therapy was left unchanged. Patients were followed in the outpatient department after 1, 3 and 6 months.

Transthoracic echocardiographic studies were performed on the day of admission and 6 months after the cardioversion. Echocardiograms were recorded with a Toshiba SSH 65A with the use of a 2.5-MHz transducer. Two-dimensional recordings were made to evaluate overall left atrial (LA) and right atrial (RA) size. Recordings were performed with the patient in the left recumbent position. The LA long-axis diameter was taken as the maximal transverse diameter, with the transducer in the standard long-axis position with a stable view of the aortic and mitral valve as well as of the ventricular septum and posterior left ventricular wall. LA and RA diameters, with the transducer at the apex of the heart, were also measured as maximal diameter at end systole with a stable simultaneous view of both valves. Atrial area was determined with the following formula: (0.5 × LA diameter in long-axis view) × (0.5 × LA diameter in apical view) × π. Echocardiographic studies were performed by 2 cardiologists who were unaware of the patient's participation in the study. LA long-axis diameter <40 mm was defined as normal. The maximum for both the apical LA and RA diameters was set at 55 mm. Using the above-mentioned formula for LA area only, values $<1{,}725$ mm^2 were considered normal.

Values are expressed as mean ± 1 standard deviation. Paired Student's t *test was used to compare data from the day of cardioversion and after 6 months of sinus rhythm. Unpaired Student's* t *test was used to compare echocardiographic data between patients with mitral valve disease, nonmitral heart disease and patients with lone AF. P values <0.05 were considered statistically significant.*

Figure 1 shows that patients with mitral valve disease had the largest mean LA area, which was significantly different from that in patients with lone AF (2592 ± 370 vs 2,004 ± 592 mm^2, $p = 0.02$). In addition, mean LA area in patients with mitral valve disease was substantially larger than it was in patients with nonmitral heart disease (2,592 ± 370 vs 2,294 ± 391 mm^2, $p = 0.05$). In the latter patient group, LA area tended to be larger than in patients with lone AF, but the difference was not statistically significant ($p = 0.08$). Six months after restoration of sinus rhythm, LA area had decreased significantly (8%) to 2,105 ± 432 mm^2 in patients with nonmitral heart disease ($p = 0.02$) and to 1,762 ± 479 mm^2 (12%) in lone AF patients ($p = 0.02$). LA area did not change in patients with mitral valve disease. For the total group, a 6% reduction of the LA area, from 2,290 ± 497 to 2,135 ± 583 mm^2 ($p = 0.03$), was found.

Figure 2 shows that the apical RA diameter was smallest in the group with lone AF (54 ± 7 mm). It was significantly smaller in this group than it was in the group with nonmitral heart disease (59 ± 6 mm, $p = 0.04$). Although patients with underlying mitral valve disease clearly had enlarged right atria (59 ± 7 mm), they did not differ significantly from the lone AF patients ($p = 0.1$). After 6 months of maintained sinus rhythm, patients with mitral valve disease and those with nonmitral heart disease showed a significant decrease in RA dimensions (11%, respectively; 8% size reduction, $p = 0.009$). This dimension remained unchanged in the group with lone AF.

At the end of follow-up all patients showed an improvement in New York Heart Association functional

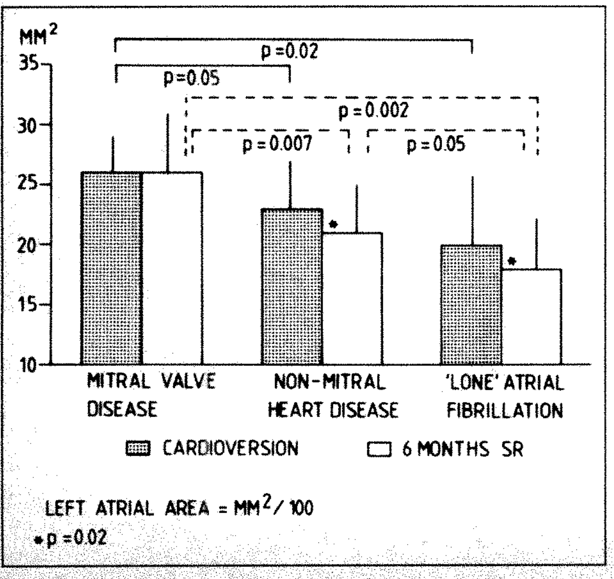

FIGURE 1. Left atrial area of the 3 patient groups at cardioversion and after 6 months of sinus rhythm (SR).

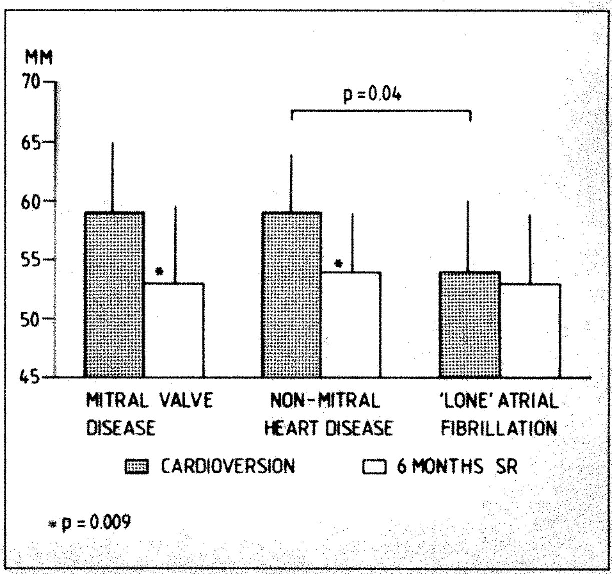

FIGURE 2. Right atrial diameter of the 3 patient groups at cardioversion and after 6 months of sinus rhythm (SR).

class: a decrease from 2.2 ± 0.6 to 1.7 ± 0.5 in patients with mitral valve disease ($p = 0.02$); a decrease from 1.6 ± 0.6 to 1.4 ± 0.6 in patients with nonmitral heart disease ($p = 0.01$); and a decrease in the lone AF group from 1.5 ± 0.5 to 1.1 ± 0.3 ($p = 0.02$).

The present study shows that after restoration and long-term maintenance of sinus rhythm, echocardiographic LA and RA dimensions may decrease. In the group of patients with lone AF, it appeared that the mean LA area nearly normalized, whereas in the other 2 patient groups the mean RA size returned to normal.

The only parameter not changed after regularization of sinus rhythm was the LA area in patients with mitral valve disease. Almost all patients included in this group had moderate-to-severe mitral valve stenosis with a rheumatic etiology. This may have precluded reduction in atrial size, because the hemodynamic consequences of obstruction of the blood flow from the atrium to the ventricle may have outweighed the beneficial effects of the restoration of the atrial systole after normalization of the rhythm. In addition, the rheumatic disease process may have caused a stiffening of the atrial wall, thereby hampering morphologic changes.

In patients with lone AF, only the left atrium was enlarged. In contrast, additional RA enlargement had occurred in both of the other patient groups. These latter groups also had the largest mean LA size. These findings suggest that after the onset of AF, altered hemodynamics will affect the left atrium first, whereas the right atrium seems to be relatively protected. Only after the development of a significant LA enlargement will left-sided hemodynamics affect RA pressure and in particular RA volume, resulting in dilatation.

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Cardiac Rhythm Precipitating Automatic Implantable Cardioverter-Defibrillator Discharge in Outpatients as Detected from Transtelephonic Electrocardiographic Recordings

Jonathan S. Steinberg, MD, and John S. Sugalski, BS

The automatic implantable cardioverter-defibrillator (AICD) has become a mainstay in the nonpharmacologic management of sustained ventricular tachyarrhythmias.[1] One of the most significant management problems for the AICD population is that of AICD discharge for cardiac rhythms other than sustained ventricular tachyarrhythmias, the rhythms that the AICD was designed to sense and terminate.[2–5] This type of AICD discharge has been termed "inappropriate," "spurious," or "false positive," can be due to a variety of cardiac rhythms, and, if recurrent, may be associated with deleterious medical or psychological consequences.[1] Although the problem clearly exists, the occurrence of inappropriate AICD discharges is difficult to define in clinical practice because the current AICD system has no internal memory or telemetry functions to document the rhythms that precipitated the AICD discharge. There is little published information that documents the cause of AICD discharges in an outpatient population. The objective of this study was to survey the records of all AICD outpatients enrolled in a transtelephonic electrocardiogram monitoring service, and to review the records for (1) the cardiac rhythms responsible for the AICD discharges, and (2) the patients' symptoms preceding the AICD discharge.

Thirty-six patients who had been enrolled in the AICD follow-up service of Medtronic Cardiocare (Forest Hills, New York) were studied. These patients were enrolled at the discretion of their primary physician, probably after ≥1 unexplained AICD discharges, and all had Ventak AICD (Cardiac Pacemakers, Incorporated, St. Paul, Minnesota) units. The patients in this program were studied with transtelephonic electrocardiographic (ECG) monitors that had looping memory capability to record data simultaneously from 2 ECG leads. When the patient activated the device to record a symptomatic episode, the previous 30 seconds of electrocardiogram were frozen in memory and an additional 45-second electrocardiogram was recorded from each of the channels. For each transtelephonic recording, the following were examined: the presence and number of AICD discharges, the cardiac rhythm and rate preceding AICD discharges, the patients' symptoms preceding AICD discharges and the cardiac rhythm following AICD discharges.

Sixteen patients did not experience an AICD discharge ($n = 12$) or did not successfully record the dis-

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charge (n = 4). Thus, data from 20 patients was available for review. Nine patients had 1 discharge episode (≥1 AICD discharge per ECG acquisition), 5 patients had 2, 3 patients had 3, and 3 patients had 4. No patient had recordings of ≥5 discharge episodes. Patients were generally enrolled for a 30-day period. Of the 36 recorded discharge episodes, there was a total of 42 actual discharges. The vast majority were recordings of a single discharge, but 4 patients had 2 consecutive discharges within seconds of one another and 1 patient had 3 consecutive AICD discharges, all within seconds.

The cardiac rhythms that were present at the time of AICD discharge are displayed in Figure 1. A variety of tachycardia rhythms were captured by transtelephonic electrocardiogram. A wide complex tachycardia considered to be ventricular tachycardia (VT) was responsible for the AICD discharge on 11 occasions in 4 patients. The VT exceeded the respective rate cutoffs of the AICD in all cases. A supraventricular tachycardia was seen on 6 occasions in 4 patients. All but 1 of the supraventricular tachycardias were sustained and all were above the respective AICD rate cutoffs. In 1 patient, paroxysmal supraventricular tachycardia self-terminated after 8 seconds to sinus rhythm, followed by an AICD discharge 6 seconds later. Rapid atrial fibrillation above the AICD rate cutoff was responsible for 5 AICD discharges in 2 patients. Sinus tachycardia with rates greater than the AICD cutoff was the cause of discharge 4 times in 2 patients. Unsustained VT of 5- and 7-seconds' duration led to an AICD discharge on 2 occasions in 2 patients. The rate of the unsustained VT was greater than the AICD rate cutoff for both patients. There were no documented examples of AICD discharges for narrow complex tachycardias with devices that had probability density function. Finally, sinus rhythm was the sole cardiac rhythm for the entire predischarge recording period on 16 occasions in 9 patients. The sinus rhythm rates were <100 beats/min in all but 1 patient in whom a rate of 105 beats/min was present. All AICD discharges were synchronous with the R wave. With 1 exception, the sinus rate was less than half the AICD rate cutoff. There were no pacemaker AICD interactions. The time after AICD implant in patients who experienced discharges was variable, ranging from 1 to 20 months, and was not clustered in the early postimplant period.

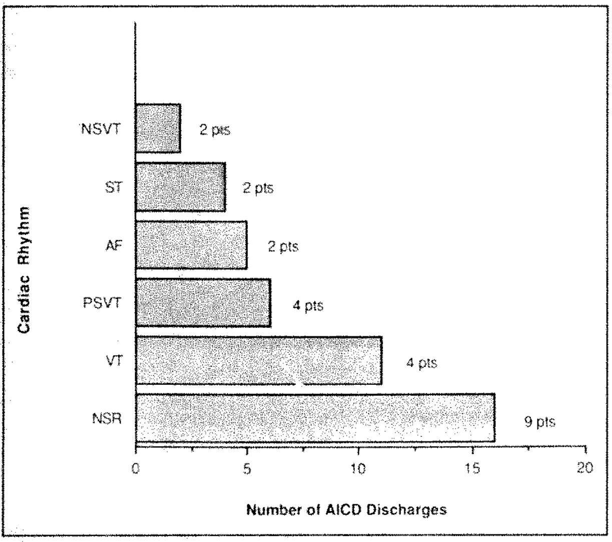

FIGURE 1. The cardiac rhythms associated with automatic implantable cardioverter-defibrillator (AICD) discharge in the 20 patients described in this report. On the *ordinate* are the cardiac rhythms responsible for AICD discharge, and on the *abscissa* are the number of recorded discharges. The number of patients for each rhythm is also indicated. See text for full description. AF = atrial fibrillation; NSR = normal sinus rhythm; NSVT = nonsustained ventricular tachycardia; PSVT = paroxysmal supraventricular tachycardia; ST = sinus tachycardia; VT = ventricular tachycardia (sustained).

Figures 2A and B provide an example of sinus rhythm present at the time of AICD discharge. Note the frequent ventricular premature complexes and ST changes that were present after the AICD discharge. The most serious postdischarge rhythm that we observed was several seconds of rapid unsustained VT in another patient. Most patients, however, had no ventricular arrhythmia after discharge.

Of the 11 episodes of VT, only 3 were associated with symptoms typical of VT. The other 8 were completely asymptomatic until AICD discharge. In these asymptomatic patients, the VT duration ranged from 12 to 15 seconds (mean 13 before the shock). In the 3 symptomatic patients, the VT duration ranged between 9 and 22 seconds (mean 14). There was no difference in VT rates between the symptomatic and asymptomatic groups. The symptoms quoted by these 3 patients were a sensation of faintness or dizziness in 2 and rapid heart beat in 1. Of the 4 patients who could not record the event, symptoms were mild or not present before AICD discharge.

The currently available AICD system will discharge after its rate, and, in some models, morphology, criteria are met. However, there is no internal memory program to document the rate and type of rhythm that precipitated AICD discharge. In addition, the current AICD generator is committed to discharge once the capacitors are charged, thereby leading to the possibility of firing after an appropriate rhythm has self-terminated. For these reasons, inappropriate discharges may occur, but the precise incidence is unknown. Previous studies have suggested a 1-year spurious discharge risk of 17%,[2] and up to 41% of AICD patients may have this problem.[1]

Ancillary methods are often relied upon to infer the appropriateness of the discharge in the absence of definite VT/ventricular fibrillation symptoms.[1,3-6] These include symptom assessment, ambulatory ECG recording, and exercise testing, as well as phonographic recording of AICD sensing tones. All have definite limitations. In this report, we describe the use of transtelephonic ECG recordings as a method of documenting the cause of AICD discharges.

The following types of rhythms that may result in an AICD discharge can be grouped: The first group are tachycardias that exceed the rate cutoff, including both sustained ventricular and supraventricular tachycardias. Under these conditions, the AICD is functioning properly. A second group are the tachycardias that self-terminate but are of sufficient duration to activate the device-charging mechanism that is then committed to fire. These rhythms are the unsustained ventricular and supraven-

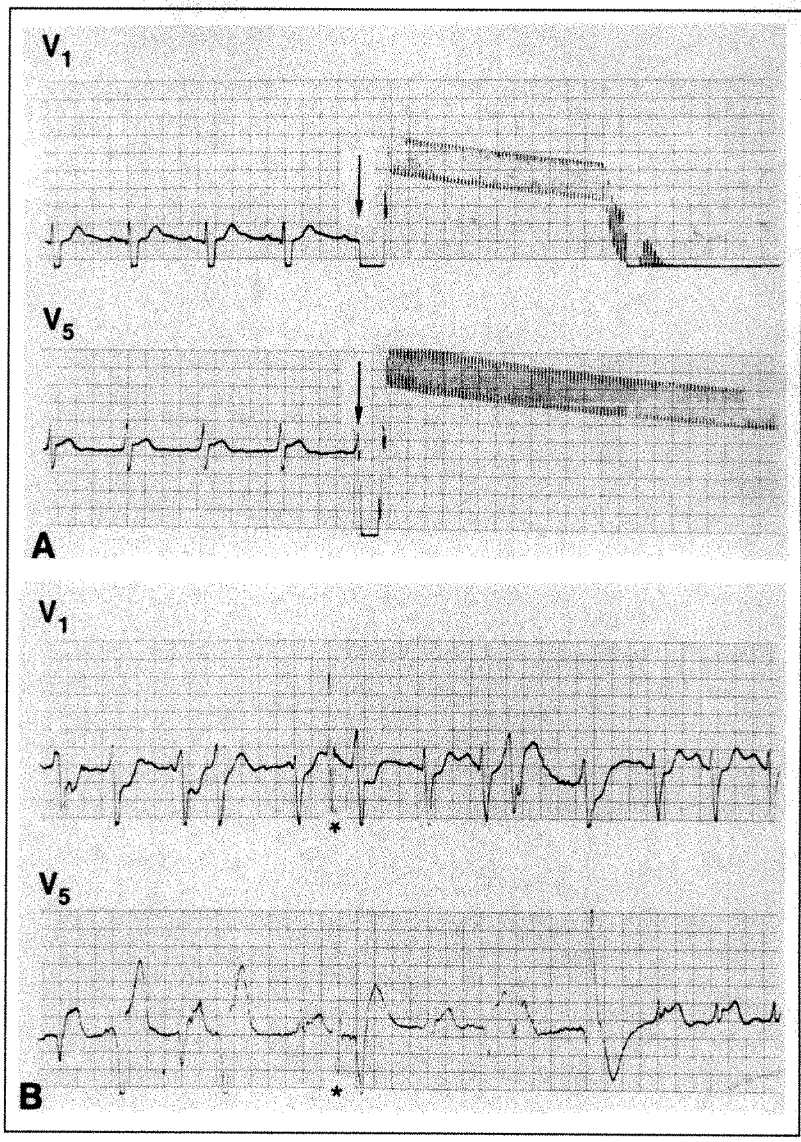

FIGURE 2. *A*, in this patient, sinus rhythm at 68 beats/min was present for the entire predischarge electrocardiographic recording period. The AICD discharge *(arrow)* occurred during sinus rhythm. A tachycardia was not present at any point in the predischarge recording. Note that the AICD discharge was synchronous with the R wave. *B*, postdischarge electrocardiographic recording is shown here for the same patient. Note that the rhythm was sinus with frequent ventricular premature beats. There were also ST-segment changes that gradually resolved over 10 to 15 seconds. The ventricular premature beats resolved within 3 to 5 seconds. The *asterisk* indicates the point where the patient triggered the recording function of the monitor.

tricular tachycardias. With the current AICD design, this is also normal AICD function. The third group are rhythms that activate the device despite not meeting the rate criterion of the individual device. Sinus rhythm would fall into this group. This type of finding indicates an abnormality of AICD sensing, such as sensing of intracardiac signals (P wave, T wave, double R wave, pacemaker stimulus), and sensing of myopotentials, lead fracture or component malfunction, or may be a manifestation of enhanced automatic gain control.

In the present study, all 3 types of cardiac rhythms that can precipitate AICD discharge were documented. Discharges for rhythms other than sustained VT or ventricular fibrillation may prompt further investigation and treatment. In addition, use of symptoms as a guide to the "appropriateness" of AICD discharge would have led to a marked underestimation of the frequency of sustained VT, thus complicating individual patient management as well as interpretation of clinical trials. Fogoros et al[2] made similar observations.

The diversity of rhythms responsible for largely asymptomatic AICD discharges described in this report suggests that ECG documentation is needed for optimal management in at least some AICD patients. Until the AICD incorporates a reliable telemetry or memory feature, external methods will be required. Because this report describes observations in a selected sample, prospective studies of unselected patients would provide more definitive data regarding the true rate of inappropriate AICD discharges.

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Captopril Versus Captopril Plus Hydrochlorothiazide for Essential Hypertension in Koreans

Daniel W. Jones, MD, and Charles D. Sands, PharmD

Among the factors that determine the response a particular patient will have to various antihypertensive drugs, racial and environmental differences are increasingly being recognized as important.[1,2] The response to angiotensin-converting enzyme inhibitors with and without a diuretic in blacks and whites is well documented.[3] However, little information is available regarding the response of Orientals.[4] This study was designed to compare captopril (Capoten®, Squibb Korea) as a single antihypertensive agent and captopril plus hydrochlorothiazide (Capozide®, Squibb Korea) in Korean patients in a double-blind, controlled clinical trial to determine if one regimen is superior to the other in terms of efficacy or subjective adverse effects, or both.

Patients included in this study were Korean men and women aged 21 to 70 years with essential hypertension and an untreated seated diastolic blood pressure (BP) of 95 to 120 mm Hg. The patients underwent a 1-week washout period before inclusion criteria were considered. They were selected from persons attending the Hypertension Clinic of Baptist Hospital, Pusan, Korea. Exclusion criteria included (1) a known hypersensitivity to either captopril or hydrochlorothiazide; (2) history of hypertensive encephalopathy or stroke within 6 months; (3) serum creatinine level >1.5 *mg/dl; (4) myocardial infarction within 6 months or angina pectoris greater than New York Heart Association class II; (5) any secondary form of hypertension; (6) diabetes mellitus requiring pharmacologic treatment; (7) patients with known gout; and (8) pregnancy, or women of child-bearing age not practicing birth control.*

BP determinations were obtained by trained observers using mercury sphygmomanometers using the fifth phase (or disappearance) of the Korotkoff sounds in the seated position. At each visit BP was checked twice at 5-minute intervals and the average recorded. BP was measured 3 to 8 hours after the daily dose of medication was taken.

Patients were treated with captopril or captopril plus hydrochlorothiazide. After a washout period of 1 week, patients whose diastolic BP ranged from 95 to 120 mm Hg and who met inclusion and exclusion criteria were randomized to 1 of 2 double-blind regimens (captopril or captopril plus hydrochlorothiazide). Visits were scheduled every 2 weeks and the study period was 8 weeks.

On the first visit (week 0), each patient was given a supply of green capsules and instructed to take 1 capsule daily 30 minutes after the morning meal. In the captopril monotherapy group the green capsule contained captopril, 25 mg, and in the captopril plus hydrochlorothiazide group it contained captopril, 25 mg, and hydrochlorothiazide, 12.5 mg. The green capsules were identical in appearance and were prepared by the Department of Pharmaceutical Services, Baptist Hospital, by pharmacists not involved in the blinded procedures. At week 4, those with a diastolic BP <90 *mm Hg continued to take 1 capsule daily and those with* >90 *mm Hg took 2 capsules daily.*

Patients were required to return their medication packets at each visit. The remaining capsules were counted and patients deemed to be compliant if they had consumed not $<80\%$ *nor* $>110\%$ *of the prescribed number of capsules. Patients were advised to limit salt intake, but no specific diet control was done.*

Differences between the 2 drug groups in BP response and changes from baseline were compared using the t *test for 2 independent samples. The chi-square test was used to compare differences between the 2 groups in terms of percentage of patients reaching the goal diastolic BP. Differences between baseline and end point BPs in each group were compared using the* t *test for paired data. All statistical calculations were performed on a microcomputer using the Patient Data Statistical Package (Simkin Inc., Gainesville, Florida).*

After a 1-week washout period, 31 patients were entered into the study. In each group, 2 were withdrawn from the study because of adverse effects and 1 was lost to follow-up in each group; 25 of the patients completed the study and are reported on here.

The 2 groups were comparable with regard to age, weight, initial systolic and diastolic BP, creatinine, glucose, cholesterol and potassium (Table I).

The BP response of the 2 groups is compared in Table II. Systolic ($p < 0.01$*) and diastolic (*$p < 0.001$*) BPs were significantly lower after initiation of either therapy. The difference in mean change in systolic and diastolic BPs between the 2 groups was significant (*$p < 0.05$ *for both).*

TABLE I Baseline Demographic Data

	Captopril (n = 13)	Captopril + HCTZ (n = 12)
Male/female	5/8	5/7
Age (year)	49 ± 5	50 ± 6
Weight (kg)	67 ± 8	66 ± 8
Systolic BP (mm Hg)	166 ± 16	174 ± 20
Diastolic BP (mm Hg)	108 ± 6	109 ± 6
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.3
Total cholesterol (mg/dl)	194 ± 34	179 ± 30
Glucose (mg/dl)	98 ± 19	109 ± 32
Potassium (mEq/liter)	4.1 ± 0.5	4.0 ± 0.4

Values are mean ± standard deviation.
BP = blood pressure; HCTZ = hydrochlorothiazide.

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The combination of captopril plus hydrochlorothiazide normalized BP (diastolic BP <90 mm Hg) in 10 of 12 (83%) compared with 4 of 13 (31%) patients in the monotherapy group ($p <0.05$).

The mean daily dose required to achieve goal BP for captopril alone (4 of 13) was 38 mg, and for captopril plus hydrochlorothiazide (10 of 12), 33 mg (difference not significant). Of the 4 patients whose BP was controlled with captopril monotherapy, 2 required 50 mg/day. Of the 10 whose BP was controlled with combination therapy, BP in 7 was controlled with captopril 25 mg plus hydrochlorothiazide 12.5 mg/day, and only 3 required captopril 50 mg and hydrochlorothiazide 25 mg/day. The mean daily dose of hydrochlorothiazide in 10 patients controlled with combination therapy was 16 mg.

In each group, 2 patients discontinued the drug owing to adverse effects: 1 in each group because of a flushing effect, 1 in the monotherapy group because of rash, and 1 in the combination therapy group from indigestion. Cough was the most frequent complaint in both groups (2 in each group) but was not severe enough to discontinue the drug in any patient.

The response of the patients in this study to captopril as monotherapy is similar to most studies reported.[5] However, the increased response with a small dose of hydrochlorothiazide is higher than that found in most studies even though the dose of hydrochlorothiazide used was much lower.[3,5,6] This large decrease in diastolic BP with captopril and low-dose hydrochlorothiazide in these Korean patients may well be explained by a high sodium intake. In another study we found a mean 24-hour sodium excretion of 233 mEq/day (16 g of sodium chloride) in 25 Korean patients after they were instructed on how to eat a low sodium diet.[4] However, this same study shows that a diuretic alone does not provide this large decrease in BP. A mean dose of hydrochlorothiazide 40 mg/day as monotherapy in 17 Korean patients only decreased diastolic BP 8.8 mm Hg.[4]

TABLE II Effects of Treatment on Blood Pressure

	Captopril (n = 13)	Captopril + HCTZ (n = 12)
Systolic BP		
Baseline	166 ± 16	174 ± 20
End	152 ± 20	138 ± 27
Diastolic BP		
Baseline	108 ± 6	109 ± 7
End	94 ± 8	83 ± 11
Change in systolic BP	−14 ± 12	−36 ± 26
Change in diastolic BP	−14 ± 7	−26 ± 13
% reaching therapeutic goal (diastolic BP <90 mm Hg)	31% (4/13)	83% (10/12)

Values are mean ± standard deviation.
BP = blood pressure; HCTZ = hydrochlorothiazide.

In Korean patients, captopril, combined with a small dose of hydrochlorothiazide, offers a significantly greater reduction in BP than captopril alone and no increase in subjective adverse effects. Combination therapy with a diuretic appears to be an ideal way to use captopril in Korean patients.

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Velocity Gradients Across Normal Cardiac Valves

Kenneth B. Gossler, BSCHe, and Stanley J. Goldberg, MD

Valvar stenoses are usually detected initially by auscultation and then confirmed by measuring a velocity gradient across a valve with Doppler echocardiography. One remaining unanswered question regards the maximal normal velocity gradient. This is a significant question since stenotic valves are associated with an increased risk of bacterial endocarditis.[1] To approach the issue of what constitutes the maximal normal velocity gradient we measured velocity gradients across valves considered by physical examination to be normal.

The study population consisted of normal healthy volunteers and patients from pediatric cardiology at the University Medical Center. Because normal cardiac valves were the subject of this study, all abnormal valves or valves that might have abnormal flows were excluded. For example, a subject with pulmonary valvar stenosis was included in the study, but data obtained from the pulmonary valve were excluded, whereas data acquired from the other 3 valves were included.

Subjects underwent standard Doppler echocardiographic examination and the velocity gradients across all 4 cardiac valves were measured according to previously described methods.[1] *Instrumentation consisted of a Hitachi CVC-151 machine and a 3.5-MHz transducer. Pulmonary valve velocity was obtained from a short-axis parasternal view. Modal peak velocity across the pulmonary valve was measured using simultaneous dual sample volumes located just proximal and immediately*

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TABLE I Mean Velocity Gradient Across the Cardiac Valves and Correlation Coefficients for Indexed Cardiac Output, Body Surface Area and Age

	Velocity Gradient			Correlation Coefficients (r value)		
Valve	Mean Peak (cm/s)	Range (cm/s)	SD (cm/s)	COI	BSA	Age
Mitral	9.3	0–25	6.4	0.06	0.17	0.23
Tricuspid	9.3	0–31	7.1	0.13	0.03	0.23
Aortic	10	0–28	7	0.03	0.25	0.25
Pulmonic	12.2	3–33	6.9	0.05	0.49	0.35

BSA = body surface area; COI = cardiac output index; SD = standard deviation.

distal to the valve. To minimize flow area effects on velocity, both sample volumes were located within the valve anulus area. The transducer was angled to align with flow as demonstrated by obtaining the highest velocity within the area of interest. Tricuspid and mitral E-wave velocities were examined similarly from the apical 4-chamber plane. Velocity gradient across the aortic valve was measured with the Biosound NDB 256 echograph, using an off-axis suprasternal notch imaging transducer with a short-axis orientation. This method allowed Doppler measurement of the left ventricular outflow tract and ascending aorta, both within the aortic anulus, parallel to blood flow. Aortic velocity gradients were not measured simultaneously because the equipment used did not have the dual sample volume capability. Accordingly, peak modal velocity was measured sequentially proximal and distal to the valve.

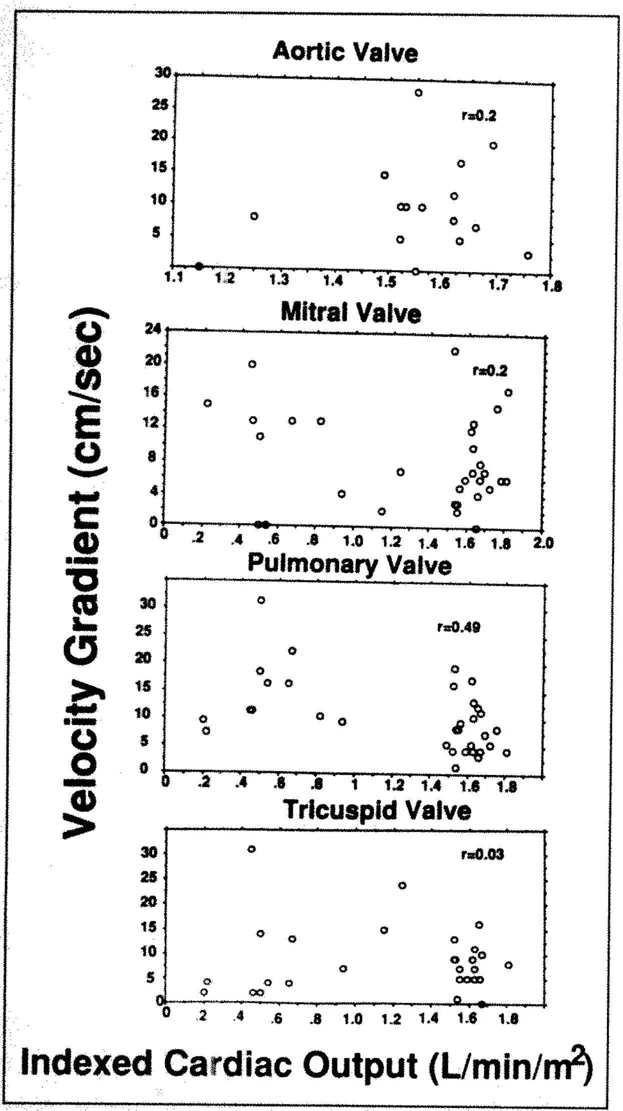

FIGURE 1. Velocity gradient compared to body surface area. Velocity gradient (cm/s) is plotted on the *vertical axes* and body surface area is plotted on the *horizontal axes*. Correlation coefficient (r) is indicated.

The ascending aorta was interrogated by Doppler echocardiography to determine the time-averaged mean velocity and the aortic diameter was measured by 2-dimensional imaging to calculate aortic output after the method of Goldberg et al.[2] If it was impossible to obtain aortic output, the pulmonary output was substituted after the method of Loeber et al.[3] Cardiac output was indexed to body surface area to compute cardiac output index.

Means and standard deviations were calculated for each cardiac valve velocity gradient. Correlation coefficients and scatter diagrams were computed for each velocity gradient compared to body surface area, indexed cardiac output and age. Analysis of variance was performed to determine if velocity gradients across the several valves were statistically different.

Forty-seven subjects (28 normal subjects and 19 with forms of congenital cardiac disease), aged 4 days to 35 years, were examined. Of these, 33 tricuspid, 36 mitral, 40 pulmonary and 18 aortic valves had velocity gradients that could be measured. Reasons for not acquiring all data from all of the subjects include (1) measurements, on review, were not obtained within the valve anulus, (2) the valve was not suitably imageable, (3) patient discomfort when trying to interrogate the aortic valve from the suprasternal notch, and (4) known abnormal valves.

Body surface area ranged from 0.20 to 1.81 m^2 (mean = 1.31). Cardiac output was measurable by Doppler in 43 of 47 subjects. Mean cardiac output indexed for body surface area was 3.1 liters/min/m^2 (range = 1.9 to 6.7). Table I contains data for each valve and Figure 1 demonstrates velocity gradient plotted against body surface area. Velocity gradients were similar for persons with no known cardiac disease and for patients with cardiac disease with normal flows through normal valves. Except for the pulmonary valve, no significant correlation was found between velocity gradients measured for any valve and body surface area, age or indexed cardiac output. For the pulmonary valve a weakly significant correlation (r = 0.49) was found between mean peak velocity gradient and body surface area.

Although no correlation of indexed cardiac output and velocity gradient was found over a normal range of outputs, velocity gradient changes would be expected with cardiac outputs beyond the normal range.

Results of this study indicate that 96% of normal cardiac valves have transvalvar velocity gradients <25 cm/s and all had a velocity gradient <33 cm/s. These results suggest that velocity gradients beyond this range, particularly those with associated auscultatory findings, are more likely to be abnormal. The study, however, does not determine the lowest velocity gradient at which a stenosis can be identified. This judgment must be made on the basis of the risk that the cardiologist wishes to take to guard against over- and underdiagnosis.

One critical aspect of measuring the velocity gradient across a valve is placing the sample volume within the valve anulus to limit, to the extent possible, effects of change in velocity as a function of change in area. For the purpose of this study, using dual sample volumes positioned under direct imaging enhanced the probability that velocity gradients were not due to area changes, because both velocities could be acquired simultaneously. Sequential measuring of velocity gradient, however, is possible but may introduce errors because of temporal variation.

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Physiologic Neuroendocrine Arousal by Mental Arithmetic Stress Test in Healthy Subjects

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Mental stress results in sympathoadrenal stimulation that may elicit or aggravate myocardial ischemia and cardiac dysrhythmias in patients with coronary artery disease.[1] A mental arithmetic stress test is a simple way to induce mild mental stress.[2,3] Several studies have examined the effects of arithmetic stress on systemic and coronary hemodynamics[3,4]; however, few studies have been reported regarding neuroendocrine and metabolic responses to arithmetic stress.[3,5] The purposes of this study were (1) to quantify the simultaneous neuroendocrine and hemodynamic responses to arithmetic stress, (2) to analyze the relation between these neuroendocrine and cardiovascular parameters in healthy volunteers, and (3) to provide insights into pathophysiologic mechanisms for the induction or aggravation of myocardial ischemia and cardiac arrhythmia during arithmetic stress.

Twenty-six healthy subjects (12 men and 14 women, mean age 52 ± 9 years) were studied. None took aspirin or any other drugs known to inhibit prostaglandin or thromboxane synthesis. Subjects refrained from smoking or caffeine-containing beverages on the day of the study. All gave voluntary, informed consent before participation in the investigation.

A Teflon™ catheter was inserted into a vein in the antecubital fossa and subjects rested in the supine posture in a quiet room at 26°C for 20 minutes before baseline data and blood samples were obtained.[6] Heart rate was determined electrocardiographically and blood pressure was assessed by mercury sphygmomanometry. Each subject performed 7 subtractions from 700 as quickly and as accurately as possible for 2.5 minutes. Blood samples were drawn without a tourniquet before and 2 minutes after subjects began serial subtractions. Measurements of systolic and diastolic blood pressure and of heart rate were made before, 1 and 2 minutes after initiation of, and after completion of the test (Figure 1). Because measurement of RR interval variation of the electrocardiogram during respiration has been reported to be a quantitative, sensitive and reproducible procedure in the evaluation of cardiac parasympathetic nervous activity,[7] the magnitude of RR interval variability was estimated by the standard deviation of the mean with an RR interval analyzer (Autonomic R-110, Fukuda Denshi). Cardiac parasympathetic activity was evaluated before, 1 minute after initiation of, and 3 minutes after completion of the test. Blood samples were

	Rest(20 min≦)	Arithmetic Stress		After Stress
		1 min	2 min	3 min
	↓	↓	↓	↓
Blood Samples	○		○	○
Blood Pressure	○	○	○	○
Electrocardiogram	○	○	○	○
CV	○	○		○

FIGURE 1. Study protocol. CV = coefficient of variation (RR-interval variability). Open circles = the times when withdrawal of blood samples, measurements of blood pressure and CV, and recording of electrocardiogram were performed.

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TABLE I Hemodynamic Changes and Neuroendocrine Arousal During Mental Arithmetic Stress Test

	Arithmetic Stress		
	Control	1 Minute	2 Minutes
Heart rate (beats/min)	69 ± 9	89 ± 17*	87 ± 16*
CV (%)	3.7 ± 1.7		4.2 ± 2.0
Systolic BP (mm Hg)	111 ± 15	145 ± 16*	142 ± 18*
Diastolic BP (mm Hg)	66 ± 8	80 ± 10*	81 ± 8*
RPP (× 10^{-2})	77 ± 15	131 ± 36*	124 ± 30*
Sodium (mEq/l)	142 ± 2		142 ± 3
Potassium (mEq/l)	3.8 ± 0.3		3.8 ± 0.2
Chloride (mEq/l)	107 ± 2		107 ± 3
Norepinephrine (ng/ml)	0.16 ± 0.10		0.25 ± 0.13*
Epinephrine (ng/ml)	0.04 ± 0.03		0.09 ± 0.07*
Glucocorticoid (μg/ml)	9.1 ± 2.3		9.7 ± 3.2
Thromboxane B_2 (pg/ml)	62 ± 28		141 ± 102*
6-keto-prostaglandin $F_{1\alpha}$ (pg/ml)	121 ± 122		122 ± 117

* $p < 0.001$ compared with control.
Values are mean ± standard deviation.
BP = blood pressure; CV = coefficient of variation (RR-interval variability); RPP = rate-pressure product.

used to measure electrolytes (Na^+, K^+, Cl^-), plasma catecholamines (norepinephrine, epinephrine), glucocorticoid, thromboxane B_2 ($n = 24$) and 6-keto-prostaglandin $F_{1\alpha}$ ($n = 21$). Electrolytes were measured by an ion-selective electrode method[8] and catecholamines by high-performance liquid chromatography.[9] Glucocorticoid was assayed by radioimmunoassay procedures, according to the method of Nakane et al.[10] Thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$, which are immediate metabolites of thromboxane A_2 and prostaglandin I_2, respectively, were measured by radioimmunoassay, according to Jaffe et al.[11] Data were expressed as the mean ± standard deviation. Statistical significances were evaluated by Student's t *test and linear regression analysis.*

Heart rate increased significantly 1 and 2 minutes after initiation of the test (both $p < 0.001$). RR-interval variability did not change during the test. Systolic and diastolic blood pressure increased significantly 1 and 2 minutes after initiation of the test (all $p < 0.001$). Rate-pressure product (heart rate × systolic blood pressure)

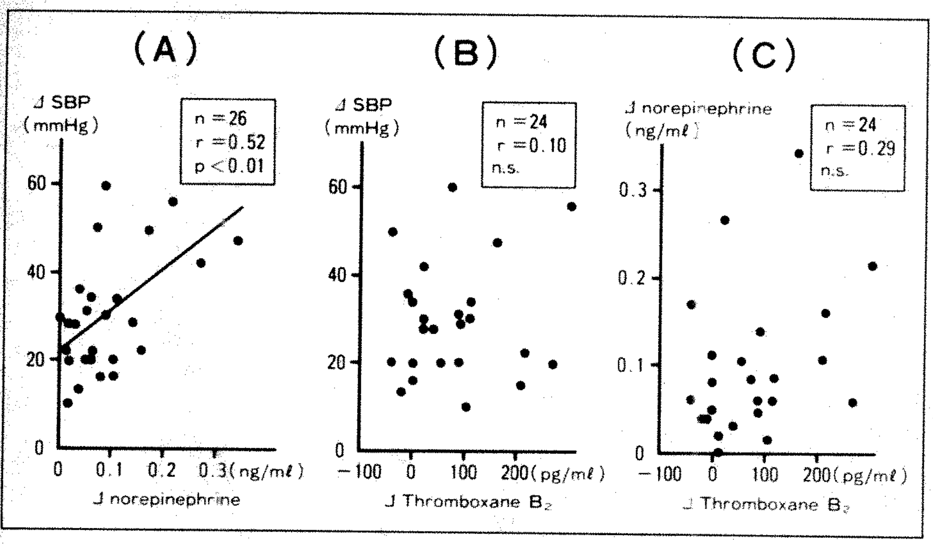

FIGURE 2. There were significant correlations ***(A)*** between the changes in systolic blood pressure (Δ SBP) and in norepinephrine (Δ norepinephrine), but ***(B)*** no significant (n.s.) correlations were observed between the changes in systolic blood pressure and thromboxane B_2 (Δ thromboxane B_2), and ***(C)*** between the changes in norepinephrine and thromboxane B_2.

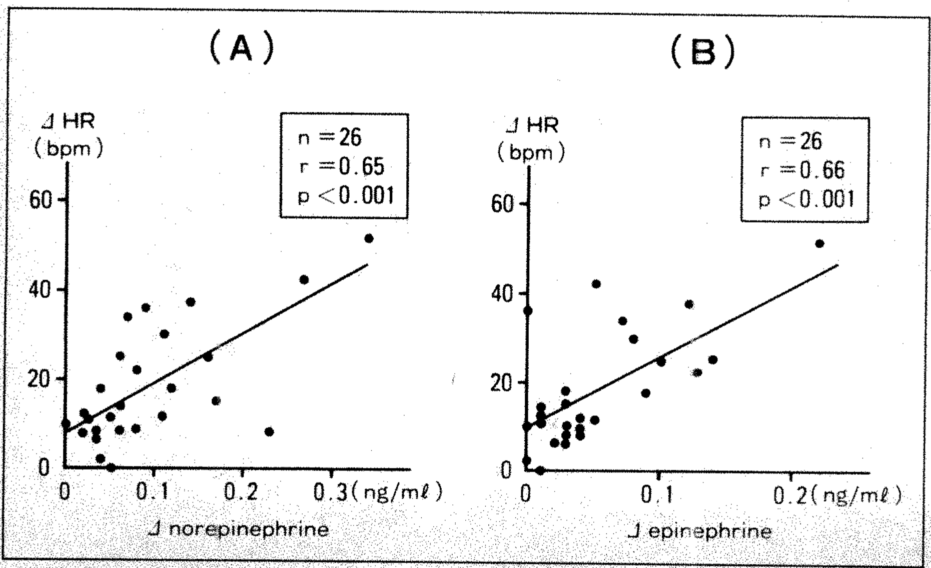

FIGURE 3. There were significant correlations ***(A)*** between the changes in heart rate (Δ HR) and norepinephrine (Δ norepinephrine), and ***(B)*** between the changes in heart rate and epinephrine (Δ epinephrine).

also increased significantly 1 and 2 minutes after starting the test (both $p < 0.001$*) (Table I). None of the electrolytes changed significantly during the test. Plasma norepinephrine and epinephrine increased significantly after initiation of the test (both* $p < 0.001$*). Plasma glucocorticoid did not change significantly during the test. Thromboxane* B_2 *increased significantly 2 minutes after starting the test (*$p < 0.001$*), but 6-keto-prostaglandin* $F_{1\alpha}$ *did not change significantly (Table I). There was a significant correlation between changes in systolic blood pressure and norepinephrine (*$r = 0.52$, $p < 0.01$*), but no significant correlation was noted between the changes in systolic blood pressure and thromboxane* B_2 *and between the changes in norepinephrine and thromboxane* B_2 *(Figure 2, A, B and C). There were significant correlations between changes in heart rate and norepinephrine (*$r = 0.65$, $p < 0.001$*) and between changes in heart rate and epinephrine (*$r = 0.66$, $p < 0.001$*) (Figure 3, A and B).*

Arithmetic stress elicited increases in heart rate (29%) and systolic (31%) and diastolic (23%) blood pressure. Rate-pressure product, an index of myocardial oxygen consumption, was also increased (71%). Kosunen[5] reported that mean heart rate increased by 19.7%, systolic blood pressure by 10.3% and diastolic blood pressure by 10.3% immediately after arithmetic stress for a period of 20 minutes. Our subjects had greater responses of heart rate and blood pressure to arithmetic stress in comparison with subjects in the aforementioned report, possibly because of different test protocols. Because RR-interval variability did not show statistically significant changes, and because there was a significant correlation between changes in heart rate and catecholamines, the enhancement of sympathetic activity seemed to play an important role in increasing heart rate during arithmetic stress.

In the present study, neuroendocrine arousal by arithmetic stress was characterized by increases in plasma norepinephrine and epinephrine, and in thromboxane B_2. Glucocorticoid and 6-keto-prostaglandin $F_{1\alpha}$ did not change significantly during the test. Adlercreutz et al[12] reported no significant change in plasma glucocorticoid after 20 minutes of arithmetic stress, which was consistent with our results. To our knowledge, there have been no reports on the effects of arithmetic stress on thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ in healthy subjects. Although Eliot and Buell[1] have reported 2 pathways of physiologic responses to stress—namely, pituitary activation—arithmetic stress according to our protocol seemed to be different from the state of vigilance normally associated with chronic stress and seemed to arouse the latter predominantly. Among the known physiologic effects of sympatheticoadrenomedullary activity, represented by catecholamines, are an increase in heart rate, elevation of blood pressure, increased platelet adhesiveness and aggregation,[13] decreased threshold to arrhythmia generation and diminished myocardial efficiency.[14] In addition, thromboxane A_2 has been reported to have a potent coronary vasoconstricting and platelet-aggregating ability and to potentiate the vasoconstrictor effect of norepinephrine.[6,15] Therefore, the neuroendocrine arousal by arithmetic stress possibly elicits not only an increase in heart rate and blood pressure but also systemic and coronary vasoconstriction and a platelet-aggregating effect, resulting in an increase in myocardial oxygen demand and a decrease in myocardial oxygen supply. Because a significant correlation was observed between changes in catecholamines and systolic blood pressure, but not between changes in thromboxane B_2 and systolic blood pressure, catecholamines seemed to play a more important role in the increase in systolic blood pressure. Our results did not show significant correlation between changes in norepinephrine and thromboxane B_2, so secretion of thromboxane A_2 seemed to be controlled not only by adrenergic stimulation but also by other factors.[6]

Our data suggest that arithmetic stress elicits increased myocardial oxygen consumption, enhanced sympathoadrenal activity and increased thromboxane A_2 synthesis. Thus, there are multiple explanations for a provocation or worsening of myocardial ischemia and dysrhythmogenesis during mental stress in patients with coronary artery disease.

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CASE REPORT

Dynamic Coronary Ostial Obstruction Due to Papillary Fibroelastoma Leading to Myocardial Ischemia and Infarction

Douglas H. Israel, MD, Warren Sherman, MD, John A. Ambrose, MD, Samin Sharma, MD, Noam Harpaz, MD, and Michael Robbins, MD

Papillary fibroelastoma is an uncommon cardiac tumor rarely diagnosed during life. Although most are incidental findings at autopsy, a small number of cases have been associated with cardiac symptoms that include angina, embolism and sudden death. We describe a case of papillary fibroelastoma detected angiographically and shown to cause coronary obstruction and myocardial ischemia.

A 50-year-old woman without coronary risk factors developed exertional chest pain 1 month before admission. Electrocardiogram was normal. On stress testing, she developed chest pain with ST-segment elevation in the inferior leads. Q-wave myocardial infarction subsequently evolved, with a peak creatine kinase of 1,188 (14.5% MB). After further episodes of chest pain at rest, the patient was referred for cardiac catheterization.

Coronary arteries were angiographically normal. After the pigtail catheter was passed into the left ventricle, the patient developed her typical chest discomfort, with inferior ST-segment elevation. Left ventriculography revealed posterobasal hypokinesia, without opacification of the right coronary artery. The right coronary artery was recannulated and selective injection filled the artery normally, but with markedly delayed distal runoff. Ostial obstruction was suspected, and an aortogram, performed to better visualize the ostium, revealed no filling (Figure 1). Several moments later, the patient's chest pain resolved and the electrocardiogram reverted to baseline. Recannulation of the right coronary artery at this time showed normal opacification and runoff. However, chest pain recurred spontaneously minutes later and repeat injection again revealed absent distal runoff. On review, the cine showed a filling defect that moved with the aortic valve and prolapsed toward the right coronary ostium. Thus, with ongoing evidence of myocardial ischemia, and a suspected aortic valve mass, the patient underwent aortic root exploration. At surgery, a pedunculated mass, 1.5 cm in diameter, was found attached to the upper margin of the right coronary cusp of the aortic valve, overlying and obstructing the right coronary ostium.

Microscopic analysis revealed a hyalinized, multilobulated pedicle with papillary fronds radiating haphazardly from its surface (Figure 2). The pedicle consisted of fused lobules of fibroelastic tissue composed of condensed, granular elastic tissue cores surrounded by lamellar whorls of elastic fibers and acellular, homogeneous collagen. The papillae were similarly organized, the coarser ones consisting of lobules of elastic tissue and collagen, and the more delicate fonds of collagen only. Each frond was invested by a single layer of flat endothelial-like cells, beneath which was a distinct light-blue myxoid layer that stained with Alcian blue.

Papillary fibroelastoma constitutes less than 1% of all primary intracardiac tumors.[1] Most often found attached to heart valves, such tumors are usually <1 cm in length, with a distinctive histologic pattern consisting of a fibrous pedicle surrounded by an arborizing pattern of villous fronds.[2] Slightly >100 cases have been published in the world,[1-3] but only a fraction have been associated with symptoms. Three cases of papillary fibroelastoma have been reported at autopsy in patients who had had a history of stroke,[3-5] although direct cause and effect relations were not proved. More convincing evidence of embolism was presented in a report of sudden death in a man with an aortic valve tumor and a left anterior descending artery embolus composed of histologically identical tissue.[6] Other cases of sudden death possibly due to coronary obstruction have been reported.[7,8] A small number of other case reports implicate papillary fibroelastoma as the cause of angina pectoris[9] or episodic cyanosis due to right ventricular outflow tract obstruction.[10]

To date, there have been 6 previously reported cases of papillary fibroelastoma detected during life,[2,11-14] usually discovered incidentally during echocardiographic investigation of other underlying cardiac disorders.[12-14] In one of the reported cases,[14] cardiac catheterization revealed an aortic root lucency in a 41-year-old man with episodes of nonexertional chest pain and angiographically normal coronary arteries. Although transient coronary ob-

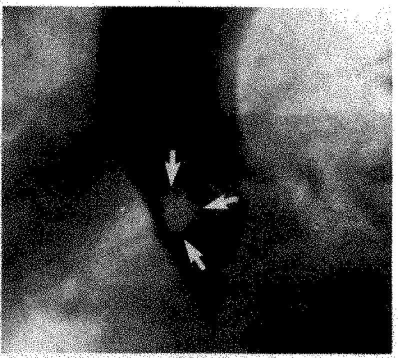

FIGURE 1. Aortogram showing a lucency in the right aortic sinus. There is no filling of the right coronary artery and on cine film lucency can be seen prolapsing in and out of right coronary ostium. When injection was made, patient had chest pain with ischemic changes on electrocardiogram.

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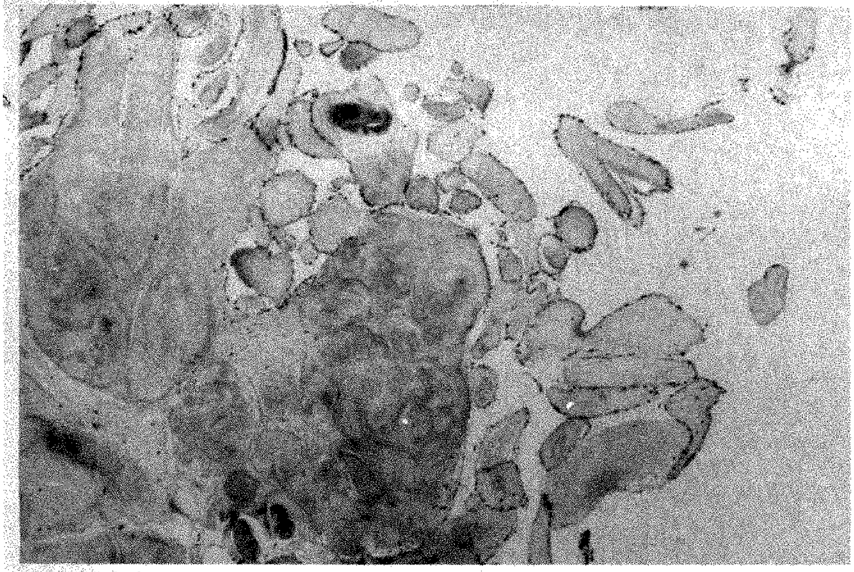

FIGURE 2. Papillary fibroelastoma consisting of thick pedicle and papillary fronds. Pedicle consists of multiple fused lobules of hyalinized connective tissue. Entire mass is invested by flat endothelial-like layer (hematoxylin-eosin stain, ×40).

struction was an obvious etiology for the patient's symptoms, at surgery one could not show mobility of the mass into either coronary ostium, in contrast to our case.

In the patient reported here, an aortic valve papillary fibroelastoma was discovered at angiography as a filling defect in the right aortic sinus. To our knowledge, this is the only case where there is definite symptomatic, electrocardiographic, enzymatic and gross intraoperative evidence of papillary fibroelastoma resulting in myocardial infarction. The actual mechanism of infarction is not entirely clear. Embolization of tumor fragments or thrombotic material cannot be excluded, but it is possible that the tumor prolapsed into the right coronary ostium, as it did during the catheterization, perhaps guided in part by the increased force and velocity of ejection of blood during the patient's exercise test. We therefore have provided for the first time definite arteriographic evidence of dynamic coronary obstruction by tumor as the cause of chest pain with electrocardiographic evidence of myocardial ischemia. As excision of such tumors is now feasible, papillary fibroelastoma should be considered as a rare but curable cause of myocardial ischemia. When indicated, 2-dimensional echocardiography and aortic root angiography may be helpful in establishing the diagnosis.

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FROM THE EDITOR

Some Good Cardiologic Books Published in 1990

1. O'Rourke RA, Pohost GM, editors. *Principles and Practice of Cardiovascular Imaging*. Boston: Little, Brown and Company, 1991:880, $175.00.

O'Rourke and Pohost, as J. Willis Hurst states, know low technology, and as this book indicates, they also know high technology. The 2 editors call this ". . . .a unique book providing comprehensive information on the sometimes confusing array of diagnostic methods for evaluation of the cardiovascular system." They may be right too.

2. Gersh BJ, Rahimtoola SH, editors. *Acute Myocardial Infarction*. New York: Elsevier, 1991:524, $84.00.

This multiauthored (49) book, the first of a new series entitled *Current Topics in Cardiology* and edited by Shahbudin H. Rahimtoola, is a comprehensive monograph on acute myocardial infarction. It is well done.

3. Gould KL. *Coronary Artery Stenosis*. New York: Elsevier, 1991:323, $99.00.

The title of this book provides little indication as to its contents. It describes pressure flow characteristics, physiologic behavior, and quantitative geometry of coronary stenoses experimentally in vivo and clinically using the most advanced invasive arteriographic analysis and noninvasive perfusion-metabolic imaging available. The first part of the book concerns anatomic and functional characteristics of coronary artery stenoses, and the second part, positron emission tomography of the heart. Although a scholarly book, it may be too "heavy" for most cardiologists.

4. Grossman W, Baim DS, editors. *Cardiac Catheterization, Angiography, and Intervention*. Fourth edition. Philadelphia: Lea & Febiger, 1991:698, $59.50.

5. Bashore TM, editor. *Invasive Cardiology: Principles and Techniques*. Toronto: B.C. Decker Inc., 1990:318, $65.00.

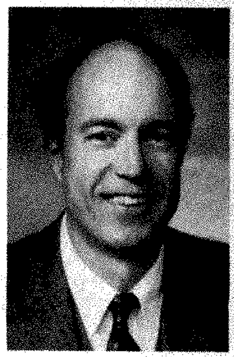
6. Serruys PW, Simon R, Beatt KJ, editors. *PTCA. An Investigational Tool and a Non-operative Treatment of Acute Ischemia*. Dordrecht: Kluwer Academic Publishers, 1990:404, $125.00.

7. Abela GS, editor. *Lasers in Cardiovascular Medicine and Surgery: Fundamentals and Techniques*. Boston: Kluwer Academic Publishers, 1990:480, $150.00.

The Grossman and Baim book has been the classic in this arena, but it is now getting some competition. It provides, as the editors state, "clear and concise descriptions of the major techniques currently used in cardiac catheterization. . .and the growing field of interventional cardiology."

The Bashore book is more expensive and contains far less information than the Grossman and Baim book.

The multiauthored Serruys et al book describes the effects of balloon-induced myocardial ischemia on the electrocardiogram, coronary blood flow dynamics, cardiac muscle metabolism, left ventricular function, and measures to counter these effects, including reperfusion, in unstable angina pectoris and acute myocardial infarction. The subject matter is of interest but the preparation of the product is not ideal. The word "Ischemia" is spelled on the title page as "Ischema."



The multiauthored Abela book describes the most up-to-date technology and procedural approaches of laser angioplasty using the various laser systems.

8. Messerli GH, editor. *Cardiovascular Drug Therapy*. Philadelphia: W.B. Saunders Company, 1990:1709, $84.00.

9. Antonaccio MJ, editor. *Cardiovascular Pharmacology*. Third edition. New York: Raven Press, 1990:556, $75.00.

The Messerli book discusses >100 cardiovascular agents and various therapeutic strategies by 184 authors. The Antonaccio book by 22 authors is a more basic pharmacologic book with less information and it costs nearly as much as the Messerli book. The Messerli book will be popular.

10. Kaplan NM. *Clinical Hypertension*. Fourth edition. Baltimore: Williams & Wilkins, 1990:466, $63.00.

11. McMahon FG. *Management of Essential Hypertension: The Once-A-Day Era*. Third edition. Mount Kisco, New York: Futura Publishing Company, Inc., 1990:684, $59.50.

The new edition of both the Kaplan and McMahon books are good. Both are single authored (which I like). The Kaplan one is my favorite despite the 220 more pages in the McMahon book for essentially the same price.

12. Grundy SM with illustrations by DuPrey LP. *Cholesterol and Atherosclerosis: Diagnosis and Treatment*. Philadelphia: J.B. Lippincott Company, and New York: Gower Medical Publishing, 1990:176, $55.00.

This book is outstanding. Its magnificent illustrations and beautiful layout make it unique and a most desirable addition to any personal or institutional cardiovascular library.

13. Davidson DM. *Preventive Cardiology*. Baltimore: Williams & Wilkins, 1991:300, $48.00.

14. Frohlich ED, editor. *Preventive Aspects of Coronary Heart Disease*. Philadelphia: F.A. Davis Company, 1990:239, $70.00. (Cardiovascular Clinics 20/3).

The Davidson book is single authored and easily readable. The Frohlich-editored book is a stronger one.

15. Gillette PC, Garson A Jr, editors. *Pediatric Arrhythmias: Electrophysiology and Pacing*. Philadelphia: W.B. Saunders Company, 1990:703, $195.00.

This textbook, by 31 authors, is probably the best thus far for diagnosis and treatment of arrhythmias in children and young adults.

16. Rosen MR, Janse MJ, Wit AL, editors. *Cardiac Electrophysiology: A Textbook Prepared in Honor of Brian F. Hoffman*. Mount Kisco, New York: Futura Publishing, Inc., 1990:1195, $160.00.

This book has contributions from 101 authors, including virtually all prominent investigators in this arena. Any book dedicated to Brian Hoffman must be a good one.

17. El-Sherif N, Samet P, editors. *Cardiac Pacing and Electrophysiology.* Third edition. Philadelphia: W.B. Saunders Company, 1991:784, $145.00.

The last edition of this book was 1980, and that book dealt only with cardiac pacing. This third edition has been much expanded by the 109 authors and is quite comprehensive.

18. Horowitz LN, editor. *Current Management of Arrhythmias.* Philadelphia: B.C. Decker, Inc., 1991:436, $75.00.

This multiauthored book summarizes recent developments in diagnosis and management of cardiac arrhythmias. Each chapter presents the views of the authors of that chapter rather than a compilation of many views.

19. Saksena S, Goldschlager N, editors. *Electrical Therapy for Cardiac Arrhythmias, Pacing, Antitachycardia Devices, Catheter Ablation.* Philadelphia: W.B. Saunders Company, 1990:731, $95.00.

This is mainly pacing but there is more. The 83 contributors represent viewpoints from 30 medical centers. A fine book.

20. Touboul P, Waldo AL, editors. *Atrial Arrhythmias. Current Concepts and Management.* St. Louis: Mosby Year Book, 1990:521, $75.00.

This book describes current concepts of the mechanisms responsible for atrial arrhythmias and their therapy by 108 contributors.

21. Hurst JW. *Ventricular Electrocardiography.* Philadelphia: J.B. Lippincott Company and New York: Gower Medical Publishing, 1991:312, $55.00.

A beautiful book stressing the vector method of interpretation of the 12-lead electrocardiogram by a masterful teacher.

22. Goldberger AL, Goldberger E. *Clinical Electrocardiography, A Simplified Approach.* Fourth edition. St. Louis: Mosby Year Book, 1990:348, $31.95.

One of the fine books from which to learn basic electrocardiography.

23. Jawad IA. *A Practical Guide to Echocardiography and Cardiac Doppler Ultrasound.* Boston: Little, Brown and Company, 1990:379, $40.00.

Another echo-Doppler book that physicians should buy, read, and then give to their echocardiography technicians.

24. Garson A Jr, Bricker JT, McNamara DG, editors. *The Science and Practice of Pediatric Cardiology.* Philadelphia: Lea & Febiger, 1990:1–668 (Volume I), 669–1616 (Volume II), and 1617–2557 (Volume III), $395.00.

These 3 volumes have it all. They require time and money. A big year for Tim Garson—2 major books in 1990.

25. Snider AR, Serwer GA. *Echocardiography in Pediatric Heart Disease.* Year Book Medical Publishers, Inc., 1990:379, $125.00.

A superb book.

26. Higgins CB, Silverman NH, Kersting-Sommerhoff BA, Schmidt K. *Congenital Heart Disease. Echocardiography and Magnetic Resonance Imaging.* New York: Raven Press, 1990:395, $135.00.

Two major diagnostic techniques from investigators in the forefront of their fields applied to a single type of cardiovascular disease—the result is an excellent product.

27. Soto B, Pacifico AD. *Angiography in Congenital Heart Malformations.* Mount Kisco, New York: Futura Publishing Company, Inc., 1990:669, $175.00.

This beautifully prepared book contains 37 chapters and 745 illustrations, most of which are angiograms, mainly axial views. This book may be the best thus far on this subject.

28. Clark EB, Takao A, editors. *Developmental Cardiology. Morphogenesis and Function.* Mount Kisco, New York: Futura Publishing Company, Inc., 1990:732, $135.00.

This monograph represents the Proceedings of the 3rd International Symposium on the Etiology and Morphogenesis of Congenital Heart Disease held in Tokyo in November 1989. The first symposium was held in 1978 and the second in 1983 and each also resulted in a book. The present book brings in "the disciplines of cellular and molecular biology, extracellular matrix, cell migration and interaction. . . ." into the morphogenesis of congenital heart disease.

29. Baumgartner WA, Reitz BA, and Achuff SE, editors, and illustrated by Schlossberg L. *Heart and Heart-Lung Transplantation.* Philadelphia: W.B. Saunders Company, 1990:406, $138.00.

30. Cooper DKC, Novitzky D, editors. *The Transplantation and Replacement of Thoracic Organs. The Present Status of Biological and Mechanical Replacement of the Heart and Lungs.* Dordrecht: Kluwer Academic Publishers, 1990:543, $225.00.

31. Thompson ME, editor. *Transplantation.* Philadelphia: F.A. Davis Company, 1990:271, $75.00.

Although the Baumgartner et al book is by 28 authors, most are from the same institution (The Johns Hopkins Medical Institutions). It is comprehensive and beautifully prepared. Some of Leon Schlossberg's drawings are in color. When a book cannot be written by a single author, a book from a single institution is advantageous. I like this book best of the cardiac transplant books thus far available. The Cooper et al and Thompson books also are good, but I prefer the book by the Baltimore group.

32. Gay WA Jr with illustrations by Roselius E. *Atlas of Adult Cardiac Surgery.* New York: Churchill Livingstone, 1990:189, $125.00.

This book contains 86 full-page drawings of various operative approaches to many *acquired* heart diseases for which surgical repair has been effective. The commentaries in the text accompanying the illustrations are brief and usually fill only a small portion of the page. The consequence is much wasted space.

33. Waldhausen JA, Orringer MB, editors. *Complications in Cardiothoracic Surgery.* St. Louis: Mosby Year Book, 1991:460, $110.00.

As Frank Spencer states in the foreword, this book is "a unique and valuable contribution in that no single book previously has concentrated in one source the available information about the numerous complications that can occur." The 86 contributors provide a valuable reference source.

34. Goldberger E. *Treatment of Cardiac Emergen-*

cies. Fifth edition. St. Louis: The C.V. Mosby Company, 1990:429, $44.95.

The topics include syncope, cardiac arrest, cardiogenic shock, arrhythmias, conduction disturbances, acute myocardial infarction, cardiopulmonary emergencies, hypertensive emergencies, aortic dissection, and cardiac tamponade, and apparatuses used for their treatment.

35. Soler-Soler J, Permanyer-Miralda G, Sagrista-Sauleda J, editors. *Pericardial Disease. New Insights and Old Dilemmas*. Dordrecht: Kluwer Academic Publishers, 1990:244, $102.50.

This book is not a comprehensive one on pericardial disease. Rather, it reviews several controversial aspects based on experiences primarily of the editors from Barcelona.

36. Bharati S, Lev M. *The Cardiac Conduction System in Unexplained Sudden Death*. Mount Kisco, New York: Futura Publishing Company, Inc., 1990:399, $115.00.

37. Rossi L, Matturri L. *Clinico-pathological Approach to Cardiac Arrhythmias—A Color Atlas*. Torino: Centro Scientifico Torinese Editore, 1990:325, $120.00.

Bharati and Lev discuss the findings in the conduction system in approximately 100 patients dying "suddenly and unexpectedly, instantaneously or within 24 hours after the onset of symptoms without any evidence of trauma" and they illustrate findings in 75 cases. These illustrations, which number 229, are almost entirely photomicrographs. The authors concluded that "the conduction system was abnormal in *all* (their italics) cases studied." The epicardial coronary arteries in their cases were "usually normal. The maximal changes were found in the bundle of His. . . ."

Rossi and Matturri also are recognized authorities on the morphologic aspects of arrhythmias and conduction disturbances. This book contains 248 color figures, also mainly photomicrographs of the conduction system. Neither book contains electrocardiograms or graphics from electrophysiologic studies. Although both are detailed anatomic descriptions of conduction tissue abnormalities, there is little in either book useful to clinical cardiologists.

38. Conti CR. *Introduction to Clinical Cardiology*. New York: Raven Press, 1991:288, $36.00.

39. Goldberger E. *Essentials of Clinical Cardiology*. Philadelphia: J.B. Lippincott Company, 1990:433, $49.95.

40. Sokolow M, McIlroy MB, Chetlin MD. *Clinical Cardiology*. Fifth edition. Norwalk, Connecticut: Appleton & Lange, 1990:659, $37.50.

41. Kloner RA, editor. *The Guide to Cardiology*. Second edition. New York: Le Jacq Communications, 1990:546, $44.00.

The Conti book is new and different. It is not intended to be as extensive as the other 3. It is quite personable, easy to read, and focuses on the appropriate approach by cardiologists to the 50 subjects under discussion. Although it is intended primarily for house officers and cardiology fellows, there are gems here for the clinical cardiologist. Chapter 2—"Communicating with Patients and Physicians"—is terrific. The usefulness or lack thereof of clinical trials is stressed. My only criticism of the Conti book would be the selection of references appearing at the end of each chapter under "Suggested Reading." More effort could have gone into selecting the most outstanding sources, including the classics, for each of the subjects under discussion.

The Goldberger book is a revision of the book, *Textbook of Clinical Cardiology*, which appeared in 1982 by the same author. The present book is half the size of the 1982 product. The Sokolow et al book is a revision of the one appearing in 1986. The Kloner-edited book is a revision of his 1984 first edition. For interns, residents, and cardiology fellows, the price of the Kloner book is $30.00. All 3 are intended primarily for non-cardiologists seeking cardiologic information.

42. Roberts WC, editor, Mason DT, Rackley CE, Willerson JT, Graham TP Jr, and Karp RB. *Cardiology 1990*. Boston: Butterworth, 1990:494, $75.00.

For some reason I continue to mention this annual book in this column every year. The book is not widely known because the publisher has few cardiology titles, the book is not presented on publishers' row at the 2 major cardiologic meetings in the USA, and maybe the authors have a few deficiencies. Nevertheless, take a peek and you will find 802 articles, each appearing in 1989, summarized, and those on the same subject are lumped together. To assist in the reading are 126 figures and 66 tables. Despite some biased views, I highly recommend this red book.

43. McDougall JA with recipes by McDougall M. *The McDougall Program. Twelve Days to Dynamic Health*. New York: NAL Books, 1990:436, $19.95.

44. Ornish D. *Dr. Dean Ornish's Program for Reversing Heart Disease*. New York: Random House, 1990:631, $24.95.

Dr. George Burch once said that "every doctor should read a diet book before he[she] retires." During the last few years I have sought out diet books and now have about 50 of them. The 2 titles above are among the better ones appearing in 1990. McDougall is the author of the 1985 book entitled *McDougall's Medicine. A Challenging Second Opinion* in which he provides the evidence for the role of dietary fat in certain cancers, osteoporosis, systemic hypertension, diabetes mellitus, certain types of arthritis, and some urinary disorders. His present book describes his 12-day plan for reversing some serious illnesses. This approach is not popular with some physicians but Dr. Nathan Pritikin was ahead of his time and persons like McDougall are similar advocates.

Ornish's 1-year study using a pure vegetarian diet plus other endeavors appeared in *Lancet* in 1990, and this book provides a step-by-step guide into his program for preventing and reversing heart disease. He is the author also of the 1982 book called *Stress, Diet & Your Heart*. McDougall and Ornish are on the right road and we need to get on it also.

William C Roberts

William Clifford Roberts, MD
Editor in Chief

The American Journal of Cardiology®

FEBRUARY 1, 1991

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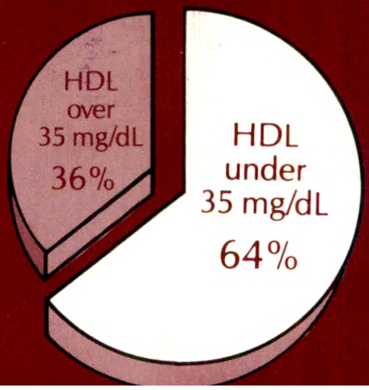
mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]

HEART ATTACK PATIENTS
(PROCAM TRIAL)[2]



PARKE-DAVIS

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The American Journal of Cardiology®

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CORONARY ARTERY DISEASE

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Complete Atrioventricular Block Complicating Inferior Wall Acute Myocardial Infarction Treated with Reperfusion Therapy

Peter Clemmensen, Eric R. Bates, Robert M. Califf, Mark A. Hlatky, Lynne Aronson, Barry S. George, Kerry L. Lee, Dean J. Kereiakes, Gerald Gacioch, Eric Berrios, Eric J. Topol, and the TAMI Study Group

The clinical implications of complete atrioventricular block complicating inferior wall acute myocardial infarction treated with reperfusion therapy were studied in 373 patients with a right coronary artery infarct. Despite initial successful reperfusion, complete AV block was frequent, and, compared with patients without complete AV block, was associated with significantly more ventricular fibrillation, sustained hypotension, congestive heart failure, pulmonary edema, impaired recovery of left ventricular function and a higher in-hospital mortality rate.

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Prognostic Importance of Delayed Q-Wave Evolution 3 to 24 Hours After Initiation of Thrombolytic Therapy for Acute Myocardial Infarction

Mark J. Eisenberg, Gabriel I. Barbash, Hanoch Hod, Arie Roth, Amir Shachar, Lea Zolti, Babeth Rabinowitz, Elieser Kaplinsky, Shlomo Laniado, and Michaela Modan

The evolution of Q waves was timed in 172 of 201 patients receiving thrombolytic therapy for a first acute myocardial infarction. Prognosis of patients with delayed Q-wave development (31) was similar to that of patients with a non-Q-wave AMI (29), with a smaller creatine kinase peak, better preservation of left ventricular function, a lower incidence of congestive heart failure and a lower in-hospital mortality rate.

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Regional Cardiac Adrenergic Function Using I-123 Meta-Iodobenzylguanidine Tomographic Imaging After Acute Myocardial Infarction

A. Iain McGhie, James R. Corbett, Marvin S. Akers, Padmakur Kulkarni, Michael N. Sills, Mark Kremers, L. Maximilian Buja, Marc Durant-Reville, Robert W. Parkey, and James T. Willerson

Regional cardiac adrenergic stores were assessed in 27 patients after acute myocardial infarction with I-123 meta-iodobenzylguanidine using a dedicated 3-detector tomograph. Data suggest that after AMI in humans (1) the abnormality in adrenergic function is more extensive than the associated abnormality in myocardial perfusion; (2) anterior wall AMI is associated with greater disruption of cardiac adrenergic function than other infarcts; (3) severity of adrenergic function correlates with degree of left ventricular dysfunction; and (4) abnormality in regional adrenergic function may be associated with presence of ventricular ectopic activity after AMI.

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Insensitivity of Noninvasive Tests to Detect Coronary Artery Vasculopathy After Heart Transplant

Frank W. Smart, Christie M. Ballantyne, Beth Cocanougher, John A. Farmer, Michael E. Sekela, George P. Noon, and James B. Young

The ability of many different studies to detect coronary artery vasculopathy was evaluated in 73 consecutive heart transplant recipients with angiographically or autopsy-proved disease (50% luminal or 70% cross-sectional narrowing). Although sensitivity of these tests was low, specificity and negative predictive value were high. Routine use of these noninvasive tests to detect coronary artery disease after heart transplant should be considered. Other noninvasive testing methods may prove more sensitive indicators of this problem.

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Comparative Effects of Overweight on Cardiovascular Risk in Younger Versus Older Men

Brent M. Egan, David R. Bassett, and Walter D. Block

The relation of age and body mass index to atherosclerosis risk factors was examined in 357 men. Data indicate that older men have greater values for several cardiovascular risk factors than do younger men. Overweight increases the prevalence of cardiovascular risk factors more in younger men.

253

Immediate and Short-Term Results of a 1988–1989 Coronary Angioplasty Registry

Francis Stammen, Jan Piessens, Matty Vrolix, James J. Glazier, Hilaire De Geest, and Jos L. Willems

The records of 507 consecutive patients undergoing a first percutaneous transluminal coronary angioplasty were reviewed. Results suggest that, despite the often advanced and anatomically complex coronary artery disease in many patients presenting at this center, favorable and immediate short-term results can be achieved, particularly with the use of a new rail-type dilatation system.

CONGESTIVE HEART FAILURE

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Sustained Reduction in Valvular Regurgitation and Atrial Volumes with Tailored Vasodilator Therapy in Advanced Congestive Heart Failure Secondary to Dilated (Ischemic or Idiopathic) Cardiomyopathy

Michele A. Hamilton, Lynne W. Stevenson, John S. Child, Jaime D. Moriguchi, Julie Walden, and Mary Woo

Acute afterload reduction therapy can improve hemodynamic function in patients with congestive heart failure, but can initial reductions in mitral and tricuspid regurgitation and atrial volumes be sustained with long-term oral vasodilator and diuretic therapy?

VALVULAR HEART DISEASE

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Frequency and Severity of Mitral Regurgitation One Year After Balloon Mitral Valvuloplasty

Ju-Pin Pan, Shoa-Lin Lin, Jorge Uy Go, Tsui-Leih Hsu, Chung-Yin Chen, Shih-Pu Wang, Benjamin N. Chiang, and Mau-Song Chang

To assess which, if any, clinical or hemodynamic variables and morphologic characteristics of the mitral valve could predict the persistence of mitral regurgitation 1 year after balloon mitral valvuloplasty, we studied 59 consecutive patients with moderate-to-severe symptomatic mitral stenosis undergoing BMV. At 1-year follow-up, some patients may have decreased severity of MR, and clinical or hemodynamic variables and morphologic characteristics did not predict the progression, or regression, of MR for any patient.

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Reference Values and Reproducibility of Doppler Echocardiography in the Assessment of the Tricuspid Valve and Right Ventricular Diastolic Function in Normal Subjects

Maurice P. Pye, Stuart D. Pringle, and Stuart M. Cobbe

Doppler echocardiographic indexes of the tricuspid and mitral valves were assessed in 74 normal subjects. A reproducibility study was also performed to examine various sources of technical and biological variability. The normal Doppler flow characteristics of the tricuspid valve are documented in detail and compared with normal mitral flow measurements in the same subject.

CARDIOMYOPATHY

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Left Ventricular Size, Mass and Function in Relation to the Duration and Quantity of Heavy Drinking in Alcoholics

Markku Kupari, Pekka Koskinen, and Antti Suokas

To assess whether the degree of alcoholic cardiomyopathy relates to the duration and severity of heavy alcohol consumption, we recorded the past and present drinking habits of 78 chronic alcoholics and compared echocardiographic data and systolic time interval determinations with those obtained from 34 healthy nonalcoholic control subjects. Although univariate analyses suggested a curvilinear relation between the duration of heavy drinking and left ventricular hypertrophy, multivariate analyses suggest that there is no simple linear dose-injury relation in the long-term cardiotoxicity of ethanol.

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Hemodynamic and Electrophysiologic Evaluation of Patients with Hypertrophic Cardiomyopathy Surviving Cardiac Arrest

Lameh Fananapazir and Stephen E. Epstein

Electrophysiologic and hemodynamic studies were performed in 30 survivors of sudden cardiac arrest with hypertrophic cardiomyopathy. These studies identify potential mechanisms for cardiac arrest in most patients with HC, and provide a critically important guide to therapy.

CONGENITAL HEART DISEASE

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Uses and Limitations of Transthoracic Echocardiography in the Assessment of Atrial Septal Defect in the Adult

Rajendra H. Mehta, Frederick Helmcke, Navin C. Nanda, Luiz Pinheiro, Tandaw E. Samdarshi, and Vinod K. Shah

Two-dimensional and color Doppler echocardiography accurately detected the presence of an atrial septal defect in 47 of 50 adults proven by surgery or cardiac catheterization. It correctly categorized all patients with ostium secundum and ostium primum ASD but misdiagnosed 3 of 5 patients with surgically proven sinus venosus ASD. Good correlation was also found between pulmonary artery systolic pressure obtained by color-guided continuous-wave Doppler and cardiac catheterization. Pulmonary to systemic blood flow ratio obtained by Doppler interrogation of right and left ventricular outflow tracts did not correlate well with cardiac catheterization results.

MISCELLANEOUS

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Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks and Whites With Systemic Hypertension and With and Without Echocardiographic and Electrocardiographic Evidence of Left Ventricular Hypertrophy

Wilbert S. Aronow, Chul Ahn, Itzhak Kronzon, and Mordecai Koenigsberg

A prospective study of elderly blacks and whites with systemic hypertension correlated the incidences of congestive heart failure, coronary events and atherothrombotic brain infarction. Incidences of CHF and coronary events were not significantly different in blacks and whites, but the incidence of ABI was 38% in blacks and 21% in whites.

CARDIOVASCULAR PHARMACOLOGY

300

Evaluation of the Pharmacokinetics and Electrocardiographic Effects of Intravenous Verapamil with Intravenous Calcium Chloride Pretreatment in Normal Subjects

Marieke Dekker Schoen, Robert B. Parker, Timothy J. Hoon, Robert J. Hariman, Jerry L. Bauman, and Karen J. Beckman

To evaluate the effects of calcium pretreatment on the disposition and electrocardiographic effects of verapamil, 8 healthy subjects received treatment in each of 3 phases—calcium, verapamil and calcium-verapamil—in a randomized, double-blind, crossover manner. In doses frequently used in a clinical setting, calcium and verapamil produced opposing effects on the sinus rate and arterial blood pressure, but not on atrioventricular conduction, indicating that the atrioventricular nodal and thus antiarrhythmic effects of verapamil are preserved despite pretreatment with calcium.

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The American Journal of Cardiology®

FEBRUARY 1, 1991, VOL. 67, NO. 4

CORONARY ARTERY DISEASE

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Complete Atrioventricular Block Complicating Inferior Wall Acute Myocardial Infarction Treated with Reperfusion Therapy

Peter Clemmensen, Eric R. Bates, Robert M. Califf, Mark A. Hlatky, Lynne Aronson, Barry S. George, Kerry L. Lee, Dean J. Kereiakes, Gerald Gacioch, Eric Berrios, Eric J. Topol, and the TAMI Study Group

The clinical implications of complete atrioventricular (AV) block complicating inferior wall acute myocardial infarction treated with reperfusion therapy were studied in 373 patients with a right coronary infarct artery. The initial patency rates of the infarct artery in patients who developed complete AV block and in those who did not were identical (90 and 91%, respectively). Despite initial successful reperfusion, complete AV block was frequent (13%) and was associated with an in-hospital mortality rate higher than that of patients without this complication (20 vs 4%, $p < 0.001$). Development of complete AV block was associated with significantly more ventricular fibrillation, sustained hypotension, congestive heart failure and pulmonary edema. Comparison between ventriculograms recorded acutely and before hospital discharge showed more impaired recovery of left ventricular function in patients with complete AV block: global ejection fraction (−3.5 vs −0.4%, $p = 0.03$) and infarct zone wall motion (−0.14 vs +0.24%, $p = 0.05$). Thus, complete AV block is an ominous sign despite initial successful reperfusion.

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Prognostic Importance of Delayed Q-Wave Evolution 3 to 24 Hours After Initiation of Thrombolytic Therapy for Acute Myocardial Infarction

Mark J. Eisenberg, Gabriel I. Barbash, Hanoch Hod, Arie Roth, Amir Shachar, Lea Zolti, Babeth Rabinowitz, Elieser Kaplinsky, Shlomo Laniado, and Michaela Modan

The timing of Q-wave evolution and its prognostic significance was studied in 201 patients who received thrombolytic therapy for a first acute myocardial infarction (AMI). One hundred forty-one patients (70%) had evidence of a Q-wave AMI within 3 hours of the initiation of thrombolytic therapy, 31 (16%) developed Q waves after 3 hours but before hospital discharge, and 29 (14%) were discharged with a non-Q-wave AMI. Prognosis of patients with delayed Q-wave development was similar to that of patients with a non-Q-wave AMI. Thus, compared to patients with early (<3 hours) Q-wave evolution, patients with delayed Q-wave evolution or

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with a non-Q-wave AMI had a smaller creatine kinase peak (mean 661 to 1,081 vs 1,251 to 1,541 IU; $p = 0.005$), better preservation of left ventricular function as measured by radionuclide ventriculography before discharge (54 ± 11% vs 47 ± 13%; $p <0.01$), a lower incidence of congestive heart failure at discharge (3 vs 15%; $p = 0.02$), and a lower in-hospital mortality rate (5 of 141 vs 0 of 60; difference not significant).

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Regional Cardiac Adrenergic Function Using I-123 Meta-Iodobenzylguanidine Tomographic Imaging After Acute Myocardial Infarction

A. Iain McGhie, James R. Corbett, Marvin S. Akers, Padmakur Kulkarni, Michael N. Sills, Mark Kremers, L. Maximilian Buja, Marc Durant-Reville, Robert W. Parkey, and James T. Willerson

Regional cardiac adrenergic stores were assessed in 27 patients after acute myocardial infarction with I-123 meta-iodobenzylguanidine (MIBG) using a dedicated 3-detector tomograph. Reduced MIBG uptake occurred in the areas of infarction (0.4 ± 0.3 counts/pixel/mCi × 103) compared with the border zones (0.6 ± 0.3 counts/pixel/mCi × 103) and the zones distant (0.9 ± 0.4 counts/pixel/mCi × 103) from the infarct zone, $p <0.001$. The MIBG defect score (52 ± 22%) was greater than the associated thallium-201 perfusion defect score (23 ± 18%, $p <0.001$). The severity of the MIBG defect score correlated inversely with the predischarge left ventricular ejection fraction, $r = -0.73$, $p <0.001$.

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Insensitivity of Noninvasive Tests to Detect Coronary Artery Vasculopathy After Heart Transplant

Frank W. Smart, Christie M. Ballantyne, Beth Cocanougher, John A. Farmer, Michael E. Sekela, George P. Noon, and James B. Young

To detect the coronary artery vasculopathy that develops frequently after heart transplant, routine surveillance noninvasive tests are often used. The ability of a variety of studies to detect coronary artery vasculopathy was evaluated in 19 of 73 consecutive heart transplant recipients with angiographically or autopsy-proved disease (50% luminal or 70% cross-sectional narrowing). Positive predictive value for coronary artery vasculopathy of gated wall motion study was 32%, Holter monitor 53%, echocardiogram 39%, exercise electrocardiogram 21%, and oral dipyridamole thallium scan 33%. Although sensitivity of these tests was low, specificity and negative predictive value was high (>75% for each test). Routine use of these noninvasive tests to detect coronary artery disease after heart transplant should be reconsidered. Other noninvasive testing modalities may prove more sensitive indicators of this problem.

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Comparative Effects of Overweight on Cardiovascular Risk in Younger Versus Older Men

Brent M. Egan, David R. Bassett, and Walter D. Block

Epidemiologic data suggest that overweight increases the risk of cardiovascular events and prevalence of hypertension more in younger than in older men. However, it is not known whether this age-related difference

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*CAPOTEN (captopril tablets) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

for the risk of overweight in men occurs with other risk factors. In this study, overweight (body mass index ≥25.5 kg/m^2) in men <45 years significantly increased the prevalence not only of hypertension but also of fasting and 1-hour hyperinsulinemia, 1-hour hyperglycemia, cholesterol values >200 mg/dl and triglyceride levels >150 mg/dl. Among men >45 years, overweight significantly increased only the prevalence of fasting and 1-hour hyperinsulinemia. These data indicate that overweight affects risk factors more adversely in younger men.

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Immediate and Short-Term Results of a 1988–1989 Coronary Angioplasty Registry

Francis Stammen, Jan Piessens, Matty Vrolix, James J. Glazier, Hilaire De Geest, and Jos L. Willems

The records of 507 consecutive patients undergoing a first percutaneous transluminal coronary angioplasty (PTCA) at our center between October 1988 and May 1989 were reviewed. Dilatation of 734 critical coronary lesions were attempted with success in 90%. The majority of these lesions (69%) were judged to be anatomically complex and dilatation of these latter lesions was performed with the rail-type system almost exclusively. Primary clinical success at angioplasty was achieved in 480 patients (95%). The event-free rate in 497 patients, followed up for a mean of 7.5 ± 1.5 months, was 72%. These observations suggest that, despite the often advanced and anatomically complex coronary artery disease in many patients currently presenting to our center for PTCA, favorable immediate and short-term results, particularly with use of the rail-type system, can be achieved.

CONGESTIVE HEART FAILURE

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Sustained Reduction in Valvular Regurgitation and Atrial Volumes with Tailored Vasodilator Therapy in Advanced Congestive Heart Failure Secondary to Dilated (Ischemic or Idiopathic) Cardiomyopathy

Michele A. Hamilton, Lynne W. Stevenson, John S. Child, Jaime D. Moriguchi, Julie Walden, and Mary Woo

To determine if initial reductions in mitral and tricuspid regurgitation and atrial volumes caused by acute afterload reduction therapy can be sustained with long-term oral therapy, 2-dimensional and color-flow Doppler echocardiography was performed in 14 patients with congestive heart failure before and after 3 ± 1 days of intensive vasodilator and diuretic therapy tailored to hemodynamic goals and again after 6 ± 2 months on an oral regimen. Mitral and tricuspid regurgitation, determined by color-flow fraction, initially decreased by a mean of 41 and 59%, respectively ($p < 0.001$); this reduction was sustained at 6 months. Significant decreases in mean left and right atrial volumes occurred with acute therapy, with further reductions at 6 months ($p < 0.001$). Congestive symptoms and signs were also markedly improved at 6 months ($p < 0.05$). In conjunction

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with clinical improvement in 6-month survivors with advanced heart failure, acute reductions in atrial volumes and atrioventricular valve regurgitation can be sustained on long-term oral vasodilator and diuretic therapy.

VALVULAR HEART DISEASE

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Frequency and Severity of Mitral Regurgitation One Year After Balloon Mitral Valvuloplasty

Ju-Pin Pan, Shoa-Lin Lin, Jorge Uy Go, Tsui-Leih Hsu, Chung-Yin Chen, Shih-Pu Wang, Benjamin N. Chiang, and Mau-Song Chang

Progressive change in mitral regurgitation (MR) after balloon mitral valvuloplasty (BMV) was evaluated by Doppler echocardiography in 59 patients with mitral stenosis. Immediately after BMV, 24 patients (41%) had no MR and in 6 patients (10%) MR remained at 1+. MR increased by 1+ in 23 patients (39%), by $>2+$ in 4 patients (6.7%) and decreased by 1+ in 2 others (3.3%). At 1-year follow-up, 1 patient required valve replacement, most patients (88%) had no further change in MR and 6 patients (10%) even showed a 1+ decrease in severity of MR when compared with results immediately after BMV. An increase of MR $\leq 2+$ is frequently seen in patients undergoing BMV, and only a small number of our patients (6.7%) developed severe MR ($\geq 3+$). Clinical or hemodynamic variables and morphologic characteristics of the mitral valve could not predict the development of significant MR after BMV.

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Reference Values and Reproducibility of Doppler Echocardiography in the Assessment of the Tricuspid Valve and Right Ventricular Diastolic Function in Normal Subjects

Maurice P. Pye, Stuart D. Pringle, and Stuart M. Cobbe

The Doppler echocardiographic indexes of the tricuspid and mitral valves were assessed in 74 normal subjects (35 women and 39 men, mean age 45 years). A reproducibility study was also performed to examine the various sources of technical and biological variability. There were significantly higher peak early and late flow velocities across the mitral valve than across the tricuspid valve (0.67 ± 0.13 and 0.47 ± 0.12 vs 0.51 ± 0.08 and 0.35 ± 0.09 $m \cdot s^{-1}$, respectively; all $p < 0.0001$). There was no significant difference between the early:late (E:A) ratios of the 2 valves (1.65 ± 0.73 vs 1.75 ± 0.67, $p < 0.1$). There was a steeper mitral early deceleration slope (-3.59 ± 1.07 vs -2.95 ± 0.91 $m \cdot s^{-2}$) but no significant difference in pressure half-times across the 2 valves (47 ± 7 vs 51 ± 12 ms, $p < 0.1$). No influence of gender or body surface area could be demonstrated. There was a weak but significant inverse relation between mitral peak early velocity and E:A ratio and age ($r = -0.39$, $p < 0.001$ and $r = -0.245$, $p < 0.01$, respectively). There was no significant correlation between any of the tricuspid flow parameters and age. The present study documents in detail the normal Doppler flow characteristics of the tricuspid valve and compares them with the normal mitral flow parameters in the same subject.

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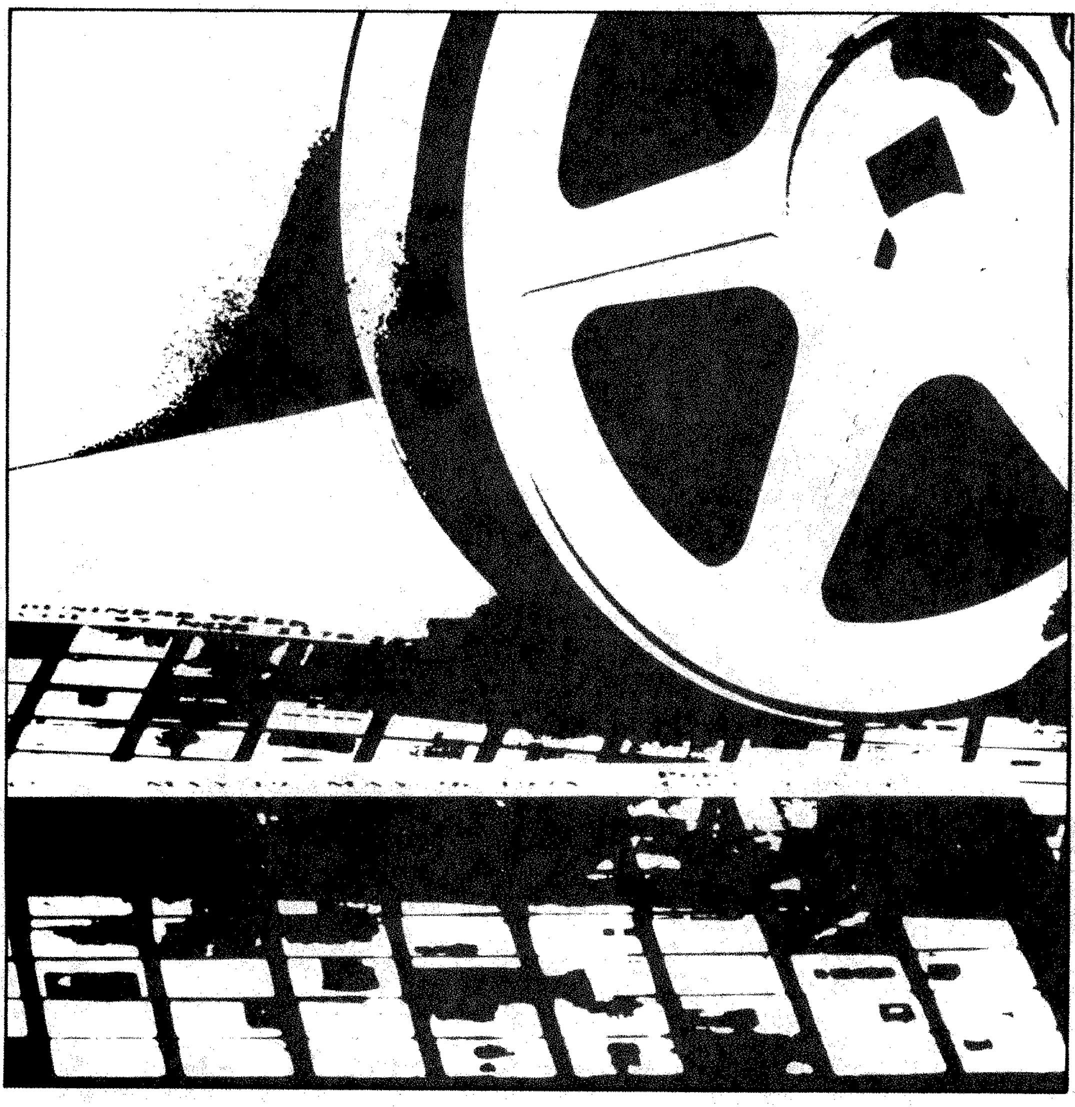

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CARDIOMYOPATHY

274

Left Ventricular Size, Mass and Function in Relation to the Duration and Quantity of Heavy Drinking in Alcoholics

Markku Kupari, Pekka Koskinen, and Antti Suokas

We studied 78 chronic alcoholics by echocardiography and systolic time intervals and recorded their past and present drinking habits to assess whether the degree of alcoholic heart muscle disease relates to the duration and severity of heavy alcohol use. The alcoholics had a higher left ventricular mass index, thicker posterior wall, longer end-systolic diameter index, and a higher preejection period/ejection time ratio than did 34 healthy nonalcoholic control subjects. In multiple linear regression analyses, these measurements were unrelated to the drinking history of the alcoholics, except that posterior wall thickness related weakly to the overall duration of heavy drinking (correlation coefficient 0.36, $p = 0.01$). Nonlinear regression methods suggested that there was, if anything, a curvilinear relation between the duration of heavy drinking and left ventricular hypertrophy and dysfunction.

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Hemodynamic and Electrophysiologic Evaluation of Patients with Hypertrophic Cardiomyopathy Surviving Cardiac Arrest

Lameh Fananapazir and Stephen E. Epstein

Electrophysiologic and hemodynamic studies were performed in 30 survivors of sudden cardiac arrest with hypertrophic cardiomyopathy. Potential causes of sudden cardiac arrest were found in all patients: (1) 21 patients (70%) had an inducible sustained ventricular arrhythmia; of these, 8 patients also had basal left ventricular outflow tract obstruction, 2 had infra-Hisian block, 1 had symptomatic sinoatrial disease, 2 had paroxysmal atrial fibrillation, and 2 had myocardial ischemia during exercise; (2) 4 had atrial tachycardia resulting in hypotension; (3) 2 had symptomatic sinoatrial disease (complicated by left ventricular outflow tract obstruction in 1); and (4) 3 had rate-related myocardial ischemia associated with hypotension. Electrophysiologic plus hemodynamic-guided therapy included implantation of a defibrillator in 19 patients, pacemaker insertion in 5 patients, verapamil and propranolol in the 5 patients with myocardial ischemia, catheter ablation of a concealed posteroseptal pathway in 1 patient and antiarrhythmic therapy in 3 patients with atrial and 4 patients with ventricular arrhythmias. During a mean follow-up period of 18 ± 19 months, 4 patients died suddenly, and 4 patients received 13 defibrillator shocks (event-free rate: 80%). Thus, electrophysiologic and hemodynamic studies reveal potential mechanisms for sudden cardiac arrest in most patients with hypertrophic cardiomyopathy, and provide a critically important guide to therapy.

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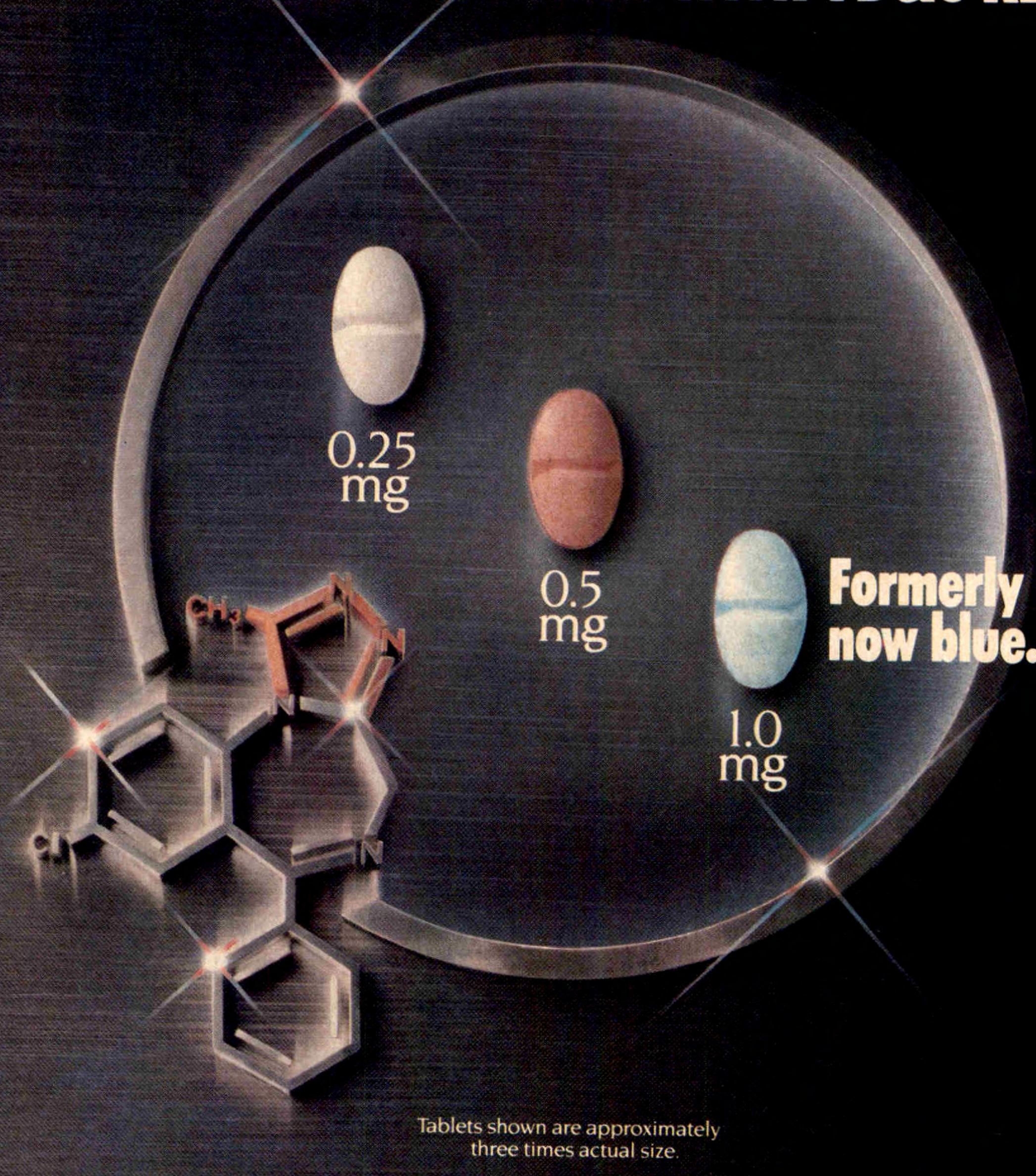

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CONGENITAL HEART DISEASE

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Uses and Limitations of Transthoracic Echocardiography in the Assessment of Atrial Septal Defect in the Adult

Rajendra H. Mehta, Frederick Helmcke, Navin C. Nanda, Luiz Pinheiro, Tandaw E. Samdarshi, and Vinod K. Shah

Two-dimensional and color Doppler echocardiography correctly categorized all ostium secundum and ostium primum atrial septal defects but misdiagnosed 3 of 5 surgically proven sinus venosus defects in 50 adults. Shunt flow volumes calculated by pulsed Doppler interrogation of color flow signals across the defect correlated fairly well with those obtained by cardiac catheterization ($r = 0.74$). Good correlation was also found between pulmonary artery systolic pressure obtained by color Doppler-guided continuous-wave Doppler and cardiac catheterization ($r = 0.89$). Pulmonary to systemic blood flow ratio obtained by Doppler interrogation of right and left ventricular outflow tracts did not correlate well with cardiac catheterization results ($r = 0.38$).

MISCELLANEOUS

295

Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks and Whites With Systemic Hypertension and With and Without Echocardiographic and Electrocardiographic Evidence of Left Ventricular Hypertrophy

Wilbert S. Aronow, Chul Ahn, Itzhak Kronzon, and Mordecai Koenigsberg

A prospective study of elderly blacks and whites with hypertension correlated the incidences of congestive heart failure (CHF), coronary events and atherothrombotic brain infarction (ABI). Follow-up was 37 months in blacks and 43 months in whites ($p < 0.01$). Incidences of CHF and coronary events were not significantly different in blacks and whites. ABI incidence was 38% in blacks and 21% in whites ($p < 0.005$). Prior CHF ($p = 0.000$), concentric LV hypertrophy ($p = 0.018$) and echocardiographic LV hypertrophy ($p = 0.022$) were independent risk factors for CHF. Echocardiographic LV hypertrophy ($p = 0.001$), serum total cholesterol ($p = 0.002$), concentric LV hypertrophy ($p = 0.005$) and prior coronary artery disease ($p = 0.042$) were independent risk factors for coronary events. Prior ABI ($p = 0.001$), echocardiographic LV hypertrophy ($p = 0.001$) and electrocardiographic LV hypertrophy ($p = 0.034$) were independent risk factors for ABI.

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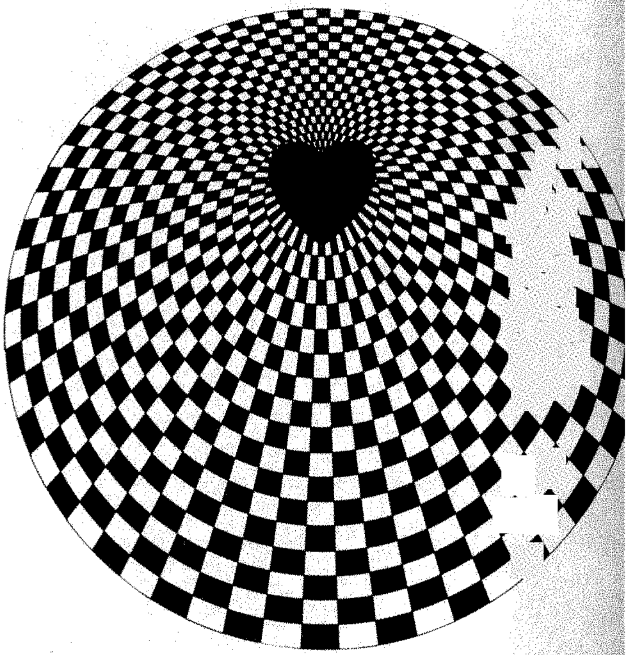

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Evaluation of the Pharmacokinetics and Electrocardiographic Effects of Intravenous Verapamil with Intravenous Calcium Chloride Pretreatment in Normal Subjects

Marieke Dekker Schoen, Robert B. Parker, Timothy J. Hoon, Robert J. Hariman, Jerry L. Bauman, and Karen J. Beckman

To evaluate the effects of calcium pretreatment on the disposition and electrocardiographic effects of verapamil, 8 healthy male volunteers received treatment in each of 3 phases in a randomized, double-blind, crossover manner: calcium, verapamil and calcium-verapamil. Blood samples for the determination of verapamil concentrations were obtained and blood pressure, heart rate and PR intervals were measured serially over 24 hours. Pretreatment with intravenous calcium did not alter the disposition of intravenous verapamil. Also, calcium had no significant effect on verapamil-induced PR prolongation. Verapamil caused a reflex increase in heart rate of similar magnitude in both phases in which it was administered. However, pretreatment with calcium caused an initial decline in heart rate, such that no verapamil-induced net change in heart rate was observed. In doses frequently used in a clinical setting, calcium and verapamil produced opposing effects on the sinus rate and arterial blood pressure, but not on atrioventricular conduction. These findings show that the atrioventricular nodal and thus antiarrhythmic effects of verapamil are preserved despite pretreatment with calcium.

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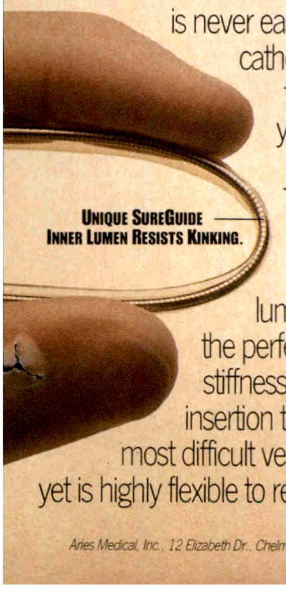

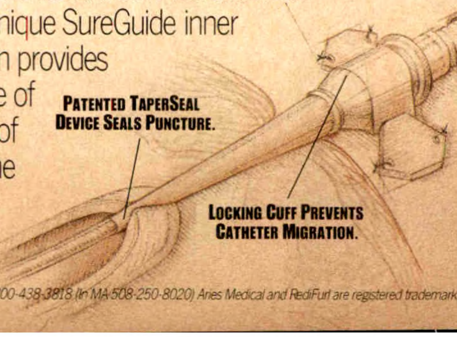
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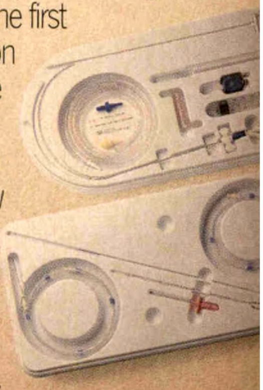

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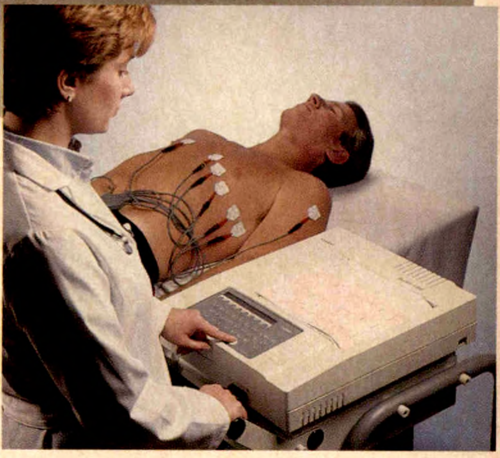

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

FEBRUARY 1, 1991, VOL. 67, NO. 4

Complete Atrioventricular Block Complicating Inferior Wall Acute Myocardial Infarction Treated with Reperfusion Therapy

Peter Clemmensen, MD, Eric R. Bates, MD, Robert M. Califf, MD, Mark A. Hlatky, MD, Lynne Aronson, BS, Barry S. George, MD, Kerry L. Lee, PhD, Dean J. Kereiakes, MD, Gerald Gacioch, MD, Eric Berrios, RN, Eric J. Topol, MD, and the TAMI Study Group*

Previous studies report larger myocardial infarcts and increased in-hospital mortality rates in patients with inferior wall acute myocardial infarction (AMI) and complete atrioventricular block (AV), but the clinical implications of these complications in patients treated with reperfusion therapy have not been addressed. The clinical course of 373 patients— 50 (13%) of whom developed complete AV block— admitted with inferior wall AMI and given thrombolytic therapy within 6 hours of symptom onset was studied. Acute patency rates of the infarct artery after thrombolytic therapy were similar in patients with or without AV block. Ventricular function measured at baseline and before discharge in patients with complete AV block showed a decrement in median ejection fraction (−3.5 vs −0.4%, p = 0.03) and in median regional wall motion (−0.14 vs +0.24 standard deviations/chord, p = 0.05). The reocclusion rate was higher in patients with complete AV block (29 vs 16%, p = 0.03). Patients with complete AV block had more episodes of ventricular fibrillation or tachycardia (36 vs 14%, p <0.001), sustained hypotension (36 vs 10%, p <0.001), pulmonary edema (12 vs 4%, p = 0.02) and a higher in-hospital mortality rate (20 vs 4%, p <0.001), although the mortality rate after hospital discharge was identical (2%) in the 2 groups. Multivariable logistic regression analysis revealed that complete AV block was a strong independent predictor of in-hospital mortality (p = 0.0006). Thus, despite initial successful reperfusion, patients with inferior wall AMI and complete AV block have higher rates of in-hospital complications and mortality.

(Am J Cardiol 1991;67:225–230)

Inferior wall acute myocardial infarction (AMI) is often complicated by atrioventricular (AV) block. Before the widespread use of thrombolytic therapy, complete AV block occurred in 8 to 13% of such patients during the hospital course.[1-3] Several investigators report that larger infarctions are associated with AV block and that a high incidence of in-hospital complications and an increased short-term mortality rate occur among patients with complete AV block.[1-3] The long-term outcome of hospital survivors, however, seems unaffected by the occurrence of complete AV block during hospitalization.[1,4] One previous study suggested that complete AV block in patients with an inferior wall myocardial infarction is associated with coexistent multivessel disease.[5] The aforementioned studies were all conducted in the prethrombolytic era. The clinical implications of complete AV block in patients treated with reperfusion therapy have not been addressed. Whether the occurrence of complete heart block is an independent risk factor for mortality has not been evaluated, because acute coronary anatomic and left ventricular function findings have not been available. We therefore undertook the present study to describe the clinical course and prognostic significance of complete AV block complicating inferior wall AMI in patients treated with reperfusion therapies.

METHODS

Patient population: The study population was culled from 810 consecutive patients who participated in 4

From the Division of Cardiology, Department of Medicine, Duke University, Durham, North Carolina; Division of Cardiology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; The Riverside Methodist Hospital, Columbus, Ohio; and the Christ Hospital, Cincinnati, Ohio. This study was presented in part at the American College of Cardiology, 38th Scientific Session, Anaheim, California, and supported in part by research grants from Genentech Inc., San Francisco, California, Abbott Laboratories, Chicago, Illinois and by Research Grants HS-05635 and HS-04873 from the Agency for Health Care Policy and Research, Rockville, Maryland, by Research Grants HL-17670 and HL-36587 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and by grants from the Robert Wood Johnson Foundation, Princeton, New Jersey. Manuscript received April 16, 1990; revised manuscript received and accepted September 26, 1990.

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*See Appendix.

clinical trials conducted by the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group, which studied different thrombolytic therapeutic strategies. Briefly, patients admitted within 6 hours of symptom onset with an AMI were enrolled if they met the following criteria: electrocardiographic evidence of epicardial injury, defined as ≥0.1 mV ST-segment elevation in ≥2 contiguous leads; absence of previous Q-wave infarction in the distribution of the acute ischemic region, and chest pain ≥30 minutes' duration unresponsive to standard sublingual nitroglycerin therapy. Patients were ineligible for the study if they had a history of a significant bleeding diathesis or a known bleeding disorder, a history of gastrointestinal or genitourinary bleeding within the preceding 4 weeks, a stroke in the past 6 months, major surgery in the preceding 2 weeks, uncontrolled hypertension (diastolic blood pressure repeatedly >110 mm Hg), other serious advanced illness, cardiogenic shock (systolic blood pressure <85 mm Hg unresponsive to volume expanders), prolonged cardiopulmonary resuscitation in the preceding 2 weeks, severe trauma within the past 6 months, psychological or physical inability to participate, or if they were women of child-bearing potential.

Patients underwent acute cardiac catheterization and the cineangiograms were recorded for later, independent analysis by a control angiographic core laboratory. The culprit infarct artery was determined to be the left anterior descending artery in 307 patients, the left circumflex artery in 104 patients and the right coronary artery in 373 patients. The remaining 26 patients had occlusion of the left main stem, or coronary bypass grafts, or the infarct artery could not be determined. Complete AV block occurred in 62 patients (8%). This complication was almost entirely limited to patients with right coronary artery-related infarction (n = 50) and rarely occurred with left anterior descending (n = 6) or left circumflex artery (n = 6) infarction. The focus of this study was therefore confined to the 373 patients with inferior wall AMI because of occlusion of the right coronary artery. Written informed consent was obtained from all patients before entry into studies. Enrollment of patients into the 4 studies began December 10, 1985, and ended March 24, 1988.

Data collection and definitions: Data pertaining to baseline characteristics, treatment and outcome were collected by research nurses and audited by a second nurse before analysis. Specific characteristics pertaining to complete heart block (duration, associated features) were collected on an ancillary data form by research nurses and fellows. Complete heart block was defined by standard clinical criteria: complete dissociation of the atrial and ventricular rates, with the atrial rate greater than the ventricular rate.

In most cases cardiac rhythm strips were available, but, in some instances, clinical observation of the cardiac monitor led to the diagnosis even though a hard copy was not available. The definitions of clinical variables have been published previously.[6-9]

Follow-up information was obtained by telephone or self-administered questionnaires given to patients or nearest relatives. The last follow-up contact occurred at a median of 22 months after hospital discharge; follow-up was 97% complete.

Thrombolytic regimen: Intravenous thrombolytic therapy was given to all patients. Of the 386 patients enrolled in the TAMI-1 trial, the first 178 patients received recombinant tissue-type plasminogen activator at a dose of 60 mg/hour during the first hour, 20 mg/hour during the second and third hours and 10 mg/hour in the last 5 hours. The remaining 208 patients received 1 mg/kg in the first hour (to a maximum dose of 90 mg), with the remainder of the dose given continuously as a 5-hour infusion for a total dose of 150 mg. All patients had 10% of the first hourly dose administered as a bolus injection over 6 minutes.[6] Of the 147 patients in the TAMI-2 study, 34 patients received 25 mg of single-chain recombinant tissue-type plasminogen activator in addition to urokinase (0.5 to 1.0 million units of urokinase). The remaining 112 patients received 1 mg/kg of tissue plasminogen activator in addition to urokinase in varying doses (0.5, 1.5 and 2.0 million units, respectively).[7] The 175 patients in the TAMI-3 study received 1.5 mg/kg recombinant tissue-type plasminogen activator. Half the patients received a bolus dose of heparin on hospital admission and all received a full dose of heparin 90 minutes after infusion of recombinant tissue-type plasminogen activator.[8] The 102 patients in the urokinase study received 3 million units over 45 to 60 minutes.[9]

Angiographic studies: All patients underwent diagnostic cardiac catheterization with angiographic visualization of all 3 major coronary arteries and a left ventriculogram ≥90 minutes after the administration of thrombolytic therapy. All patients received 5,000 units of intravenous heparin subsequent to arterial access. Quantitative estimation of the flow in the infarct-related coronary artery was performed by Thrombolysis in Myocardial Infarction (TIMI) classification criteria.[10] Arteries with TIMI flow grade 0 or 1 were considered occluded and arteries with flow grade 2 or 3 were considered patent. Reocclusion was defined in patients not occluded upon leaving the diagnostic catheterization as recurrent total occlusion of the infarct-related artery. Lesion location was defined as proximal or distal in relation to the first right ventricular branch of the right coronary artery. Percutaneous transluminal coronary angioplasty was performed when anatomically feasible in all patients with a TIMI flow grade of 0 to 1. Patients with TIMI flow grade 2 or 3 underwent percutaneous transluminal coronary angioplasty in accordance with the different protocols (by randomization in TAMI-1, and if clinical evidence of ongoing ischemia persisted in TAMI-2, TAMI-3 and the urokinase study). When acute percutaneous transluminal coronary angioplasty was performed, an additional 5,000 units of heparin were given. In patients with angiographically visible filling defects suggesting the presence of residual thrombus, 30 mg of intracoronary recombinant tissue-type plasminogen activator or 300,000 units of intracoronary urokinase were administered. An effort was made to perform a repeat cardiac catheterization in

TABLE I Baseline Characteristics of 373 Patients with Right Coronary Artery Infarct Events

	Complete AVB (n = 50)	No Complete AVB (n = 323)
Age (median, interquartile range)	60 (53–66)	57 (49–64)
Male gender (%)	37 (74)	257 (80)
History of smoking (%)	31 (62)	217 (67)
Diabetes (%)	10 (20)	41 (13)
Family history of CAD (%)	19 (38)	153 (47)
Hypertension (%)	19 (38)	136 (42)
Hyperlipidemia (%)	4 (8)	43 (13)
History of angina (%)	19 (38)	151 (48)
Time to Rx (median in minutes, interquartile range)	159 (120–197)	170 (122–214)
Multivessel disease* (%)	15 (30)	133 (42)

* ≥75% stenosis of ≥2 major epicardial coronary arteries.
AVB = atrioventricular block; CAD = coronary artery disease; Rx = thrombolytic therapy.

all patients as close as possible to the seventh day after hospital admission. Global left ventricular ejection fraction was determined by the area-length method[11] and regional wall motion of the infarct zone by the centerline chord method.[12] Both the acute and predischarge angiographic studies were analyzed at the angiographic core laboratory by independent observers.

Hospital care: All patients were admitted to the coronary care unit, where cardiac rhythm was routinely monitored for 24 hours. Medical therapy included intravenous lidocaine for 24 hours, 1 enteric-coated aspirin tablet (325 mg) per day and diltiazem (60 mg) every 6 hours for 7 days. Heparin was administered by intravenous infusion up to 7 days to a level of activated partial thromboplastin time 1.5 to 2.5 times greater than control values. Beta blockers were only administered when clinically indicated (supraventricular tachycardia, hypertension or angina pectoris). All additional revascularization procedures, including percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, were performed as clinically indicated at the discretion of the attending physician. Temporary transcutaneous[13] or transvenous pacemakers were used at the discretion of the treating physician.

Data analysis: Unless otherwise indicated, all continuous variables describing patient characteristics were described in terms of the median and interquartile range. Discrete variables were described by frequencies and percentages. Group differences in proportions were examined with the chi-square test. Patient groups were compared with respect to continuous variables by the 2-sample Wilcoxon rank-sum test. Two-sided p values <0.05 were considered statistically significant. Multiple logistic regression analysis was performed to determine the importance of complete AV block as a predictor of in-hospital mortality relative to other prognostic clinical and angiographic variables.

RESULTS

Complete AV block was observed in 50 of the 373 patients (13%) with an AMI related to the right coronary artery. No substantial differences in clinical baseline characteristics were found between the 2 groups (Table I), although the patients with complete AV block did appear to have a slightly lower percentage of multivessel disease and a lower percentage of a history of angina pectoris.

TABLE II Clinical Characteristics of Complete Atrioventricular Block in 50 Patients Treated with Reperfusion Therapy

Duration in hours (median, interquartile range)	2.5 (1–12)
Precipitating clinical events (%)	19 (38)
Reperfusion (%)	5 (10)
PTCA (%)	7 (14)
Reocclusion (%)	7 (14)
Immediate complications of AVB	
Hypotension (%)	35 (73)
VT/VF (%)	10 (20)
Asystole (%)	8 (17)

PTCA = percutaneous transluminal coronary angioplasty; VT/VF = ventricular tachycardia and ventricular fibrillation; other abbreviations as in Table I.

Figure 1 shows the time from onset of chest pain to the first recorded episode of complete AV block. In 54% of patients, complete AV block was present on admission and developed in all except 2 patients within 72 hours after symptom onset. Immediate treatment of complete AV block included temporary pacemakers in 60% of the patients. In 8%, the pacemaker was inserted prophylactically, before the development of complete AV block. Atropine was administered to 82% of the patients with complete AV block. The block was transient in all but 1 patient, who required insertion of a permanent pacemaker after aortocoronary bypass surgery. Duration of complete AV block was ≤1 hour in 25% of the patients and <12 hours in 75% (median duration 2.5 hours). Complete AV block could be associated with chemical reperfusion, angioplasty or reocclusion in 38% of patients (Table II). Immediate complications associated with the development of complete AV block occurred often and included hypotension, ventricular tachycardia, ventricular fibrillation and asystole.

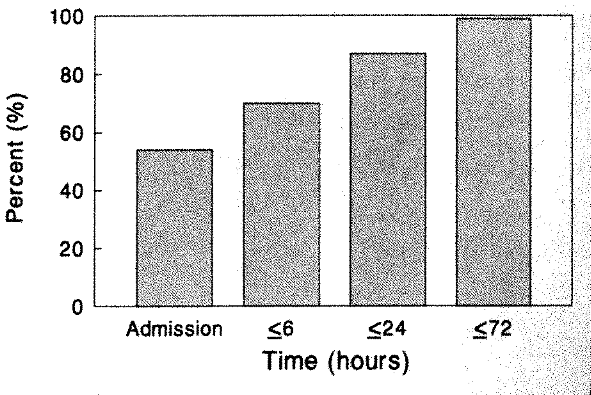

FIGURE 1. Cumulative percentage of patients developing complete atrioventricular block ≤6, 24 and 72 hours after onset of myocardial infarction.

TABLE III Infarct Artery Status

	Complete AVB (n = 50)	No Complete AVB (n = 323)
Proximal lesion (%)	28 (56)	144 (45)
Distal lesion (%)	22 (44)	179 (55)
Acute findings (%)		
90-min patency*	33 (66)	222 (69)
Acute PTCA	24 (48)	129 (40)
Final patency†	45 (90)	294 (91)
Predischarge findings		
Patency (%)	27 (71)	226 (82)
Reocclusion (%)	13 (29)	46 (16)

* First diagnostic angiogram.
† Final patency = infarct artery patency status after acute pharmacologic and mechanical interventions.
Abbreviations as in Tables I and II.

TABLE IV Clinical Outcomes

	Complete AVB (n = 50)	No Complete AVB (n = 323)	p Value
VT/VF (%) (Unrelated to bradycardia)	18 (36)	46 (14)	<0.001
Sustained hypotension (%)	18 (36)	33 (10)	<0.001
Congestive heart failure (%)	13 (26)	17 (5)	<0.001
Pulmonary edema (%)	6 (12)	13 (4)	0.02
In-hospital mortality (%)	10 (20)	12 (4)	<0.001
Long-term mortality (%) (22-month follow-up)	1 (2)	6 (2)	NS

NS = not significant; other abbreviations as in Tables I and II.

The infarct artery status is summarized in Table III. There was no difference between the patency of the infarct artery after thrombolytic therapy and the patency after acute catheterization: 90% in patients with and 91% in those without complete AV block. However, patency before hospital discharge was 11% lower in the patients with complete AV block because of a higher reocclusion rate (29 vs 16%, p = 0.03).

Global and regional left ventricular function data are shown in Figures 2 and 3. At acute angiography, the mean ejection fraction in the group with complete AV block was 56%, compared with 55% in the group without. At follow-up angiography, there was no change in the ejection fraction in patients without complete AV block, but there was a 3.5% decrease in the group with complete AV block (p = 0.03). The mean acute infarct zone wall motion was −2.49 standard deviations/chord with complete AV block and −2.39 standard deviations/chord without. Before discharge, acute infarct zone wall motion improved in the group without complete AV block and decreased further in the group with complete AV block. The trend toward more functional recovery of the infarct zone among patients without complete AV block was of borderline statistical significance (p = 0.05).

The clinical outcomes of the 2 groups are listed in Table IV. The in-hospital course was more complicated in the patients who developed complete AV block. Ventricular fibrillation or tachycardia occurred in 36 vs 14% and sustained hypotension in 36 vs 10%, respectively. Ten of the 50 patients with complete AV block (20%) died in-hospital versus only 12 of 323 without (4%) (p <0.001). The long-term mortality rates of the hospital survivors after a median follow-up of 22 months were identical (2%) in the 2 groups.

The independent prognostic value of complete AV block was examined by logistic regression analysis. When age, acute left ventricular ejection fraction, number of diseased vessels and TIMI grade flow were entered into a multivariable logistic regression model, complete AV block contributed independent prognostic information concerning in-hospital mortality (chi-square = 11.6, p = 0.0006).

DISCUSSION

The major finding of this study was that the incidence of complete AV block in patients with AMI treated with thrombolytic therapy is similar to the incidence reported before the thrombolytic era.[1-3,5,14] Furthermore, when compared with historical populations, the mortality rate in the group of patients who developed complete AV block was not lower, despite aggressive reperfusion attempts, usually with success in this population.[1-3,14,15] Our findings of a somewhat more depressed regional and global left ventricular function are

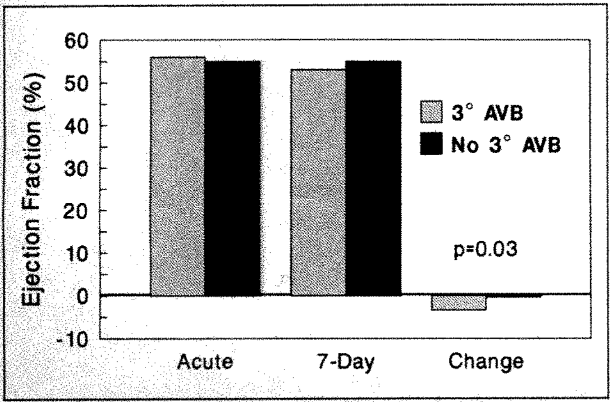

FIGURE 2. Global left ventricular ejection fraction as determined by contrast ventriculography for the 2 groups. Values represent means of paired acute and predischarge studies. AVB = atrioventricular block.

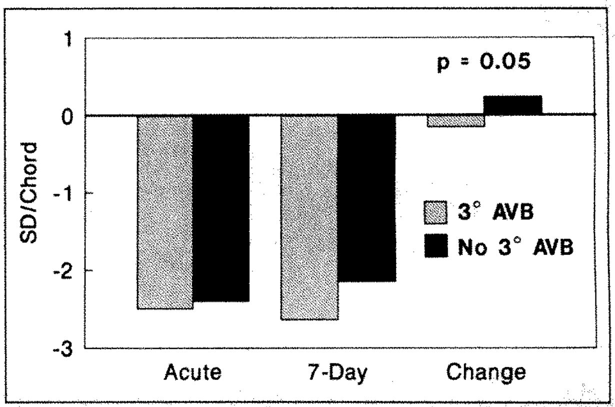

FIGURE 3. Regional wall motion of the infarct zone as determined by the centerline chord method for the 2 groups. Values represent means of paired acute and predischarge studies. SD = standard deviations; other abbreviation as in Figure 2.

in agreement with those of previous studies that describe larger infarcts and more depressed left ventricular function in the patients who developed complete AV block compared with those who did not.[1–3,15]

A recent study by Nicod et al[1] involving patients who did not undergo thrombolytic intervention found that complete AV block was an independent factor for in-hospital prognosis when correcting for other noninvasive factors known to be important for prognosis. This finding was confirmed in the present study, where complete AV block was a strong predictor of in-hospital mortality, even after considering variables obtained via cardiac catheterization, including acute left ventricular ejection fraction, number of diseased vessels and TIMI grade flow after thrombolytic therapy. Long-term prognosis of hospital survivors was good in the present study and unaffected by the development of complete AV block in the hospital. Other studies conducted in the prethrombolytic era have reported similar results.[1,16]

In the present as well as in previous studies, complete AV block was transient in almost all patients.[1,3,17] According to Hackel et al,[18] the transient nature of complete AV block in these patients is probably due to the relative resistance of the conduction system to ischemia. These investigators summarized several mechanisms that, alone or in combination, could cause transient complete AV block in these patients, all of which could be altered by myocardial reperfusion. Reperfusion could diminish the severity of local metabolic changes and the total duration of ischemia of the AV node. Conversely, restoration of anterograde blood flow to previously ischemic myocardium might both facilitate leukocyte migration to the infarcted area and stimulate vagal nerve endings in the inferoposterior aspects of the left ventricle.[18] Based on the findings in the present study, it appears that the major effect of reperfusion on the natural history of complete AV block is to minimize its duration, possibly because the ischemic burden on the AV node is relieved. Indeed, the 2.5-hour median duration of the 3° AV block in this study is the shortest ever reported in a large series of patients.

In the present study, complete AV block was associated with an active component of reperfusion therapy (reperfusion, angioplasty or reocclusion) in 38% of patients, raising the possibility that reperfusion could itself provoke the AV block. Clinicians should thus be prepared for this complication to arise when other clinical markers of reperfusion occur, when angioplasty is chosen as an adjunctive therapy or when the patient develops clinical signs of reocclusion.

A recent study hypothesized that patients who develop acute AV block have a high incidence of multivessel disease, particularly co-existing obstruction of the left anterior descending artery.[5] That study comprised only 51 patients, and the 32 patients with $\geq 75\%$ stenosis of the left anterior descending artery had a 31% incidence of AV block versus a 1% incidence among the patients without significant disease of that artery. Our findings are in agreement with another recent large study of 749 patients, which failed to detect such a relation.[1]

Study limitations: The ideal study design for answering the question of the impact of 3° AV block on patient outcome after thrombolytic therapy would include a control group not undergoing any clinical attempt at myocardial reperfusion. However, such a study would be almost impossible to conduct in the present era, and our comparisons are therefore limited to findings of previous studies conducted before the widespread use of reperfusion therapies. The clinical definition of AV block used in this study is not as complete as what could be achieved by continuous Holter monitoring of a large population. Transient episodes of complete AV block could have been missed, or, in some cases, AV dissociation could have been erroneously labeled as heart block. Nevertheless, these findings are representative of current practice in institutions with a full-time cardiology staff observing patients with AMIs. Also, the critical question of right ventricular involvement in patients with complete AV block cannot be answered by the present study, because right ventricular infarction was not routinely assessed in this population. A previous study has found that the right ventricle is involved in the majority of patients with inferior wall myocardial infarction who develop advanced AV block.[15]

Acknowledgment: We are indebted to Galen S. Wagner, MD, for valuable advice and critical review of this manuscript, and to Lisbeth Mattisson and Sandy Pendergraph for expert manuscript preparation.

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APPENDIX

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Prognostic Importance of Delayed Q-Wave Evolution 3 to 24 Hours After Initiation of Thrombolytic Therapy for Acute Myocardial Infarction

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The timing of Q-wave evolution and its prognostic significance was studied in 201 patients who received thrombolytic therapy for a first acute myocardial infarction (AMI). One hundred forty-one patients (70%) had evidence of a Q-wave AMI within 3 hours of the initiation of thrombolytic therapy, 31 (16%) developed Q waves after 3 hours but before hospital discharge, and 29 (14%) were discharged with a non-Q-wave AMI. Laboratory indicators of myocardial damage and in-hospital morbidity and mortality were greater among patients with Q-wave AMIs than with non-Q-wave AMIs. When these indexes were examined with respect to the timing of Q-wave evolution, the prognosis of patients with delayed Q-wave development was similar to that of patients with non-Q-wave AMIs. Thus, compared to patients with early (≤3 hours) Q-wave evolution, patients with delayed Q-wave evolution or with a non-Q-wave AMI had a smaller creatine kinase peak (mean 661 to 1,081 vs 1,251 to 1,541 IU; $p = 0.005$), better preservation of left ventricular function as measured by radionuclide ventriculography before discharge (mean ± standard deviation 54 ± 11% vs 47 ± 13%; $p < 0.01$), and a lower incidence of congestive heart failure at discharge (3 vs 15%; $p = 0.02$). In-hospital mortality was lower among patients with delayed Q-wave evolution or with a non-Q-wave AMI (5 of 141 vs 0 of 60; difference not significant). It is possible that delayed (>3 hours) evolution of a Q-wave AMI among patients receiving thrombolytic therapy may represent the higher prevalence of patients with an incomplete AMI in this population.

(Am J Cardiol 1991;67:231–235)

Numerous studies demonstrate the prognostic importance of Q waves that appear after an acute myocardial infarction (AMI). These studies show that in-hospital morbidity and mortality are higher in patients with a Q-wave AMI than in patients with a non-Q-wave AMI.[1–4] Despite the short-term advantage held by patients with a non-Q-wave AMI, long-term morbidity and mortality for both groups are similar.[5–8] This similarity in long-term prognosis is the result of a higher rate of late cardiac events among patients with non-Q-wave AMIs.[9–11] Cardiac catheterization data show that patients with non-Q-wave AMIs are less likely than those with Q-wave AMIs to have completely occluded coronary arteries and are more likely to have significant collateral circulation.[12–16]

However, it is important to note that most studies that investigated Q-wave appearance and its prognostic significance took place before thrombolytic therapy for AMI became widespread. In this study, we examined the timing of Q-wave evolution in 201 patients who received thrombolytic therapy for a first AMI. Our purpose was to identify whether thrombolytic therapy alters the known prognostic significance of Q-wave versus non-Q-wave AMI and to determine the prognostic importance of the timing of Q-wave evolution.

METHODS

Patient population: Two-hundred fifty-three consecutive patients with an AMI were treated with thrombolytic therapy. Entry criteria were: age <73 years, severe chest pain for ≥30 minutes but ≤6 hours, and ST-segment elevation of 0.1 mV in ≥2 contiguous electrocardiographic leads. Exclusion criteria were left bundle branch block on the initial electrocardiogram, diastolic blood pressure >120 mm Hg, a history of congestive heart failure, previous cardiac surgery, concurrent terminal illness, or a predisposition for bleeding that would contraindicate thrombolytic therapy. Of the 253 patients initially enrolled, 42 were subsequently excluded because of a historical AMI that could have influenced Q-wave interpretation. An additional 10 patients were excluded because of missing electrocardiograms that precluded evaluation of the timing of Q-wave appearance. Thus, a total of 201 patients treated with thrombolytic therapy for a first AMI were available for study.

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Of these, 147 received recombinant tissue-type plasminogen activator and 54 received streptokinase.

Medical treatment: Patients treated with recombinant tissue-type plasminogen activator (G11035, Boehringer Ingelheim, Federal Republic of Germany) received a total dose of 100 to 120 mg over 3 to 6 hours. Patients treated with streptokinase received 1.5 million U over 30 to 60 minutes. All patients received oral aspirin in a dose of 250 mg/day, and most received heparin intravenously or subcutaneously. Patients also received additional therapy for individual clinical conditions (e.g., antianginal, anticongestive or antiarrhythmic treatment).

Electrocardiographic studies: Electrocardiograms were recorded continuously during the first hour after the initiation of thrombolytic infusion and every 3 hours thereafter until the end of the first 24 hours, after which 12-lead electrocardiographic tracings were obtained daily. For the purpose of analysis, electrocardiograms were recorded at 4 time points: just before thrombolytic therapy, 3 hours after treatment was initiated, 24 hours after the start of treatment, and at hospital discharge. Q waves were defined by the following 3 criteria: duration ≥ 0.04 ms, presence in electrocardiographic leads where ST segments were originally elevated, and either a height $>\frac{1}{3}$ of the R wave in 1 lead or a new appearance in 2 geographically similar leads.

Coronary angiography and angioplasty: After thrombolytic therapy, patients were treated conservatively. Routine cardiac catheterizations were not performed; coronary angiography was performed only if the patient had postinfarction angina or hemodynamic instability during hospitalization or if a predischarge exercise test provoked severe myocardial ischemia.

Patency of the coronary arteries was evaluated in the laboratories of each participating medical center and by a consensus reading of all angiograms by the same 2 coronary angiographers, who were blinded to the clinical course of the patients, except for the electrocardiographic location of the infarction. Severity of coronary artery disease was determined by visual assessment of the reduction in luminal diameter (percent stenosis) and by Thrombolysis in Myocardial Infarction[17] gradings of perfusion for each coronary artery and its major branches.

Patients with $>50\%$ reduction in the luminal diameter of the infarct-related artery underwent ad hoc percutaneous transluminal coronary angioplasty, unless the infarct artery was considered insignificant, the lesion was considered unsuitable for angioplasty for other reasons, or the patient was referred to coronary bypass surgery because of 3-vessel coronary artery disease or left main artery disease or its equivalent.

Laboratory studies: Serial blood samples were collected for creatine kinase determinations at the onset of thrombolytic treatment and every 3 hours for the first 24 hours. Radionuclide ventriculographic studies were performed as soon as possible after admission and again just before hospital discharge.

Follow-up: Follow-up clinic visits were scheduled at 2, 6 and 12 months after hospital discharge. Physical examinations were performed and information collected on pertinent clinical outcomes (e.g., reinfarction, rehospitalization, invasive procedures). Treadmill effort-tolerance tests and radionuclide ventriculographic stress studies were conducted at the 2-month follow-up visit. A test was defined as positive when at least 1 of the following symptoms occurred: typical ischemic chest pain, ≥ 2-mm ST depression 0.08 second after the J point, or a decrease of 15 mm Hg in blood pressure from baseline level.

Statistical methods: The patient population was divided into 4 groups according to the time of Q-wave appearance. In the 2 "early" groups, the Q wave appeared before thrombolytic treatment or ≤ 3 hours after treatment began. In the 2 "delayed" groups, the Q wave appeared >3 hours after treatment began or patients were discharged with a non-Q-wave AMI. Because each of the 2 early groups and each of the 2 delayed groups resembled each other with respect to baseline characteristics as well as to clinical and laboratory outcomes, they were presented separately in the tables but grouped in all statistical analyses.

Data were analyzed with BMDP software (Biomedical Computer Programs, University of California, Berkeley). Group characteristics were expressed as mean ± standard deviation for continuous variables or as rates for categorical variables. Univariate comparisons between the early and delayed groups were tested by chi-square or by Fisher's exact test, when appropri-

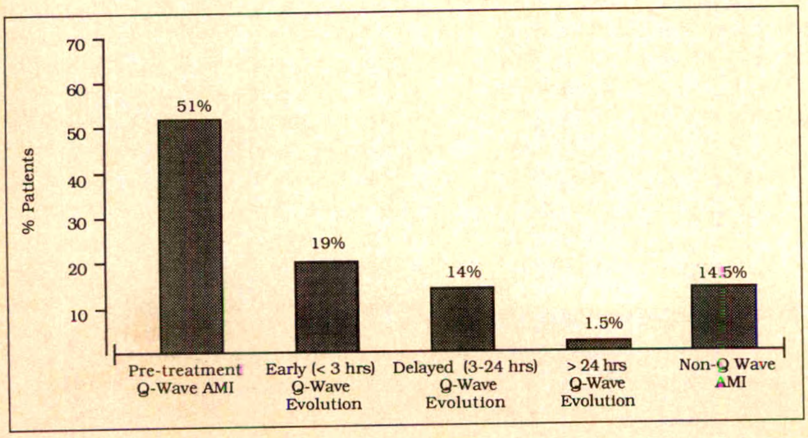

FIGURE 1. Timing of Q-wave evolution.

TABLE I Baseline Characteristics of Patients Analyzed with Respect to Timing of Q-Wave Appearance

	Early Group		Delayed Group		
	Pretreatment Q-Wave AMI (n = 103)	(≤3 hrs) Q-Wave AMI (n = 38)	(>3 hrs) Q-Wave AMI (n = 31)	Non-Q-Wave AMI (n = 29)	Early vs Delayed Group (p Value)
Age (yr ± SD)	58 ± 10	59 ± 9	59 ± 13	57 ± 11	0.73*
Sex (% male)	77	89	81	76	0.92†
Anterior AMI (% pts)	59	55	42	66	0.63*
Preinfarction angina pectoris (% pts)					
<7 days	20	26	23	24	
>7 days	23	16	23	17	0.95†
Smoking within last 3 wks (% pts)	45	42	74	45	0.06†
Diabetes mellitus (% pts)	13	18	16	24	0.41†
Hypertension (% pts)	23	24	13	14	0.15†
Killip class at admission (% pts)					
1 + 2	94	92	97	100	0.14‡
3 + 4	6	8	3	0	
Time to treatment (min ± SD)	153 ± 96	125 ± 66	133 ± 63	152 ± 75	0.76*

* By *t* test.
† By chi-square.
‡ By Fisher exact test.
AMI = acute myocardial infarction; SD = standard deviation.

ate, for categorical variables, and by *t* test for continuous variables. Overall multivariate comparisons between each of the 2 early groups and each of the 2 delayed groups, and overall comparison between the early and delayed groups, accounting simultaneously for all baseline and outcome variables, were performed by Hotelling T^2 test (BMDP program 3D).

RESULTS

Figure 1 shows the timing of Q-wave appearance among the 201 patients. Q waves were present in 103 patients (51%) before initiation of thrombolytic therapy (pretreatment Q-wave evolution). Thirty-eight patients (19%) developed Q waves during the 3 hours after treatment began (early Q-wave evolution), and in 28 patients (14%) Q waves developed 3 to 24 hours after the treatment began (delayed Q-wave evolution). For the purpose of analysis, the 3 patients (1.5%) who developed Q waves after 24 hours but before discharge were added to the delayed Q-wave evolution group, which then comprised 31 patients. At discharge, 29 patients (14.5%) still had no evidence of Q waves and were defined as having non-Q-wave infarctions. Multivariate analysis, comparing each of the 2 early groups and each of the 2 delayed groups to each other, accounting simultaneously for all baseline and outcome variables, indicated no significant differences between the number of each pair (p = 0.55 and p = 0.49, respectively). Consequently, all further statistical analyses were based on comparisons of the combined early to the combined delayed groups.

Baseline characteristics are listed in Table I. One hundred sixty patients (mean age ± standard deviation 58 ± 10 years) were men (79.6%) and 41 were women (20.4%). One hundred fourteen patients (56.7%) had an anterior AMI. The average time between the onset of chest pain and thrombolytic treatment was 145 ± 84 minutes. There were no significant differences between the early and delayed groups with regard to age, gender, infarct site, diabetes mellitus, systemic hypertension, antecedent angina, time from onset of pain to treatment, or Killip class at admission. There were more smokers in the delayed group, and this excess approached significance (p = 0.06).

The delayed group was characterized by lower peak (p = 0.04) and cumulative 24-hour creatine kinase levels (p = 0.08) (Table II). Results of radionuclide ventriculographic testing paralleled these findings; left ventricular ejection fractions at hospital admission and discharge were highest in patients with delayed or no Q-wave evolution. This difference approached significance (p = 0.06) only with respect to left ventricular ejection fraction at discharge.

Clinical evidence of myocardial damage, as evidenced by congestive heart failure at discharge, was also significantly less frequent (p = 0.03) among patients with delayed or no Q-wave evolution. The rate of in-hospital clinical reinfarction was similar in the 2 groups.

Table III lists the frequency of in-hospital coronary angiography and angioplasty among the 4 patient groups. Both cardiac catheterization (p = 0.13) and coronary angioplasty (p = 0.04) were performed more frequently among patients with delayed or no Q-wave evolution.

Follow-up data analyzed with respect to the timing of Q-wave appearance are listed in Table IV. Radionuclide stress ventriculography was performed 2 months after study enrollment. There was a significant increase in left ventricular ejection fraction after exercise among patients with delayed Q-wave evolution, whereas there was no change or a slight decrease in left ventricular ejection fraction in the early group (p = 0.01). At the 1-

year follow-up, the rate of rehospitalization for cardiac causes was similar among the 4 groups (data not shown).

Early Q-wave evolution was associated with a nonsignificant increase in hospital mortality (p = 0.17). All 5 patients who died during initial hospitalization belonged to the early Q-wave evolution group. However, the 2 patients who died after discharge belonged to the delayed group. Thus, overall 1-year mortality was similar in the 2 groups. Finally, multivariate comparison be-

TABLE II In-Hospital Indexes of Myocardial Damage

	Early Group		Delayed Group		
	Pretreatment Q-Wave AMI (n = 103)	(≤3 hrs) Q-Wave AMI (n = 38)	(>3 hrs) Q-Wave AMI (n = 31)	Non-Q-Wave AMI (n = 29)	Early vs Delayed Group (p Value)
Peak CK (IU/liter)	1,251 ± 841	1,341 ± 841	1,081 ± 1,071	661 ± 662	0.04*
Cumulative 24-hour CK release (IU/liter)	6,528 ± 3,965	6,692 ± 4,069	4,239 ± 2,578	3,942 ± 3,409	0.08*
In-hospital reinfarction no. (% pts)	15 (15)	10 (26)	4 (13)	3 (10)	0.39†
Admission LVEF (no.)%	(87) 48 ± 14	(34) 47 ± 14	(24) 52 ± 14	(28) 53 ± 12	0.27*
Discharge LVEF (no.)%	(98) 47 ± 13	(32) 47 ± 13	(27) 53 ± 11	(28) 54 ± 11	0.06*
LVEF change	−1.0 ± 11	−0.4 ± 9	−1.7 ± 11	+0.6 ± 8	0.26*
CHF at discharge no. (%)	18 (17)	3 (8)	1 (3)	1 (3)	0.03‡

* By *t* test.
† By chi-square.
‡ By Fisher exact test.
AMI = acute myocardial infarction; CHF = congestive heart failure; CK = creatine kinase; LVEF = left ventricular ejection fraction.

TABLE III Results of In-Hospital Invasive Procedures

	Early Group		Delayed Group		
	Pretreatment Q-Wave AMI (n = 103)	(≤3 hrs) Q-Wave AMI (n = 38)	(>3 hrs) Q-Wave AMI (n = 31)	Non-Q-Wave AMI (n = 29)	Early vs Delayed Group* (p Value)
Coronary angiography performed no. (%)	35 (34)	13 (34)	14 (45)	14 (48)	0.13
Patent infarct artery no. (%)	27 (77)	11 (85)	12 (86)	12 (86)	0.69
Coronary angioplasties performed no. (%)	11 (11)	10 (26)	10 (32)	7 (24)	0.04

* By chi-square.
Abbreviation as in Table II.

TABLE IV One-Year Follow-Up Data

	Early Group		Delayed Group		
	Pretreatment Q-Wave AMI (n = 103)	(≤3 hrs) Q-Wave AMI (n = 38)	(>3 hrs) Q-Wave AMI (n = 31)	Non-Q-Wave AMI (n = 29)	Early vs Delayed Group (p Value)
Stress ventriculography at 2 mos.					
Rest % LVEF	54 ± 11	50 ± 11	54 ± 8	52 ± 10	0.97*
Stress % LVEF	53 ± 17	50 ± 11	57 ± 9	56 ± 12	0.23*
LVEF change	−1.3 ± 12	0.0 ± 8	+2.3 ± 5	+4.0 ± 5	0.01*
Recurrent AMI no. (% pts)	3 (3)	3 (8)	2 (6)	2 (7)	0.34†
Frequency of mechanical revascularization					
Coronary angioplasty no. (% pts)	1 (1)	4 (10)	2 (6)	(0)	0.65†
Coronary bypass surgery no. (% pts)	9 (9)	3 (8)	1 (3)	3 (10)	0.45†
In-hospital mortality (% pts)	2	8	0	0	0.17‡
Mortality during 1-year follow-up (% pts)	0	0	3	3	0.09†
Total mortality (% pts)	2	8	3	3	0.65†

* By *t* test.
† By Fisher exact test.
‡ By chi-square.
Abbreviations as in Table II.

tween the early and delayed groups, accounting simultaneously for all baseline and outcome variables, was significant (p = 0.003).

DISCUSSION

Our results indicate that the prognostic value of a Q-wave AMI in predicting in-hospital clinical outcome in patients with AMI receiving thrombolytic therapy is similar to that documented by studies from the prethrombolytic era.[18,19] Thus, hospital morbidity and mortality rates were higher for our patients with a Q-wave AMI than for patients with a non-Q-wave AMI. Although rates of rehospitalizations and recurrent AMIs were similar among our 4 patient groups, the only 2 patients who died after discharge had either a non-Q-wave or a delayed Q-wave AMI. Consequently, although hospital mortality was higher for the patients with an early Q-wave AMI, 1-year mortality was similar for all groups. This finding agrees with earlier observations in the general AMI population, in which post-discharge recurrent AMI and sudden death occur more frequently in patients with a non-Q-wave AMI.[7,8]

In addition to the aforementioned groups of patients with early ($\leq$3 hours) Q-wave evolution (70%) and patients discharged with a non-Q-wave AMI (19%), we identified a group of patients with delayed (>3 hours) Q-wave development that comprised 16% of our patient population. These patients appeared to be prognostically similar to patients with a non-Q-wave AMI with respect to both clinical and laboratory indexes of myocardial damage.

Our findings thus suggest that, in addition to the traditional stratification of patients into Q- versus non-Q-wave AMI groups, the timing of Q-wave appearance should be emphasized in patients with an AMI receiving thrombolytic therapy, and that a delayed evolution of a Q-wave AMI in these patients predicts an outcome similar to that of patients with a non-Q-wave AMI. Nevertheless, because of the limited number of patients in these 2 groups (60), a larger population may be required to verify this finding.

It is possible that our patients with delayed Q-wave evolution had a better prognosis because their coronary anatomy (lower grade coronary occlusion and increased collateralizations) was similar to that of patients with a non-Q-wave AMI.[12-16] Because the appearance of a Q-wave infarction depends on the amount and site of myocardial necrosis, it is possible that, like patients with a non-Q-wave AMI in whom the amount of myocardium destroyed is insufficient for a Q wave to evolve, patients with delayed Q-wave evolution also had a smaller infarct. Thus, thrombolytic intervention has curtailed the process of myocardial necrosis, resulting in slower Q-wave evolution. It is possible, therefore, that delayed Q-wave evolution may be more prevalent among patients with an AMI who are treated with thrombolytic therapy and who therefore have a higher incidence of incomplete infarcts.

Acknowledgment: We wish to thank Lisa Underhill for skillful help in editing this manuscript, and Boehringer Ingelheim, Federal Republic of Germany, for supplies of recombinant tissue-type plasminogen activator.

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Regional Cardiac Adrenergic Function Using I-123 Meta-Iodobenzylguanidine Tomographic Imaging After Acute Myocardial Infarction

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The effect of acute myocardial infarction (AMI) on regional cardiac adrenergic function was studied in 27 patients mean ± standard deviation 10 ± 4 days after AMI. Regional adrenergic function was evaluated noninvasively with I-123 meta-iodobenzylguanidine (MIBG) using a dedicated 3-detector tomograph. Four hours after its administration, there was reduced MIBG uptake in the region of infarction, 0.38 ± 0.31 counts/pixel/mCi × 103 compared with 0.60 ± 0.30 counts/pixel/mCi × 103 and 0.92 ± 0.35 counts/pixel/mCi × 103 in the zones bordering and distant from the infarct area, respectively, $p < 0.001$. In all patients, the area of reduced MIBG uptake after 4 hours was more extensive than the associated thallium-201 perfusion defect with defect scores of 52 ± 22 and 23 ± 18%, respectively, $p < 0.001$. After anterior wall AMI, the 4-hour MIBG defect score was 70 ± 13% and the degree of mismatch between myocardial perfusion and MIBG uptake was 30 ± 9% compared with 39 ± 17 and 21 ± 17% after inferior AMI, $p < 0.001$ and $p = 0.016$, respectively. The 4-hour MIBG defect score correlated inversely with the predischarge left ventricular ejection fraction, $r = -0.73$, $p < 0.001$. Patients with ventricular arrhythmia of ≥1 ventricular premature complexes per hour, paired ventricular premature complexes or ventricular tachycardia detected during the late hospital phase had higher 4-hour MIBG defect scores, 62.5 ± 15.0%, than patients with no detectable complex ventricular ectopic activity and a ventricular premature complex frequency of <1 per hour, 44.6 ± 23.4%, $p = 0.036$. These data suggest that after acute AMI in humans (1) the abnormality in adrenergic function is more extensive than the associated abnormality in myocardial perfusion; (2) anterior wall AMI is associated with greater disruption of cardiac adrenergic function than other infarcts; (3) the severity of cardiac adrenergic dysfunction correlates with the degree of left ventricular dysfunction; and (4) the abnormality in regional adrenergic function may be associated with the presence of ventricular ectopic activity after AMI.

(Am J Cardiol 1991;67:236–242)

Meta-iodobenzylguanidine (MIBG) is a norepinephrine analog that is not metabolized by either monoamine oxidase or catechol-O-methyl transferase. It competes for the same uptake mechanism (uptake-1) that transports norepinephrine into the sympathetic nerve terminals.[1,2] MIBG can be labeled with iodine-123 allowing cardiac adrenergic neuronal function to be evaluated.

This technique has been used in humans to evaluate cardiac adrenergic function in normal control subjects[3-5] and has also demonstrated abnormalities in patients with ventricular dysfunction secondary to congestive cardiomyopathy.[6,7] I-123 MIBG has also been used to detect regional sympathetic denervation[8,9] in the dog. Minardo et al[8] demonstrated denervation after acute myocardial infarction (AMI). In addition, it was shown that the area of denervation was more extensive than the associated area of infarction and that the area of normally perfused but denervated myocardium with absent MIBG uptake was suprasensitive to adrenergic stimulation.

Prognosis after AMI is known to be related to the degree of left ventricular dysfunction and the presence of ventricular arrhythmias.[10-12] Abnormalities in cardiac adrenergic function occur with heart failure[13-17] and have been implicated as a possible contributing mechanism to arrhythmogenesis.[18-21]

In this study, we determined what effect AMI had on regional cardiac adrenergic function in humans and tested the following hypotheses: (1) The extent of regional adrenergic dysfunction is greater than the area of infarct; (2) the severity of the abnormality in cardiac adrenergic function correlates with the severity of left ventricular dysfunction after AMI; and (3) the extent of

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TABLE I Clinical Characteristics of Patients Studied

Pt. No.	Age (yr) & Sex	MI Site	VPC/ hr	Complex Vent. Ect.	LVEF (%)	DM	SH	Beta Blocker	CA	Nitr.	ACE Inhib.	Diur.	Antiarrhyth.
1	51M	I	11	0	59	0	0	0	+	0	0	0	0
2	56M	I	88	Paired VPC	—	0	0	0	0	0	0	0	0
3	42M	I	<1	0	63	0	0	0	0	0	0	0	0
4	47M	I	—	0	71	0	0	0	0	0	0	0	0
5	52F	I	<1	0	67	0	+	+	0	0	0	0	0
6	39M	I	<1	0	55	0	0	0	0	0	0	0	0
7	68F	I	<1	0	67	0	0	+	0	0	0	0	0
8	40F	A	<1	0	48	0	0	0	0	0	+	0	0
9	60F	A	<1	0	52	+	+	0	0	+	0	0	0
10	71F	I	4	0	70	0	+	0	+	+	0	0	0
11	48F	A	1	0	42	0	0	+	0	0	+	0	0
12	64F	A	<1	0	70	0	+	+	0	0	0	0	0
13	54M	I	<1	0	62	+	0	0	0	0	0	0	0
14	37M	I	—	0	60	0	0	0	0	0	+	0	0
15	63M	I	<1	0	53	+	0	0	+	+	0	0	0
16	61F	A	<1	0	20	0	+	+	0	+	+	+	0
17	69F	A	<1	0	45	+	0	+	0	0	0	0	0
18	67F	I	255	Paired VPC	47	+	0	0	+	+	0	0	P
19	55M	I	<1	0	49	0	0	0	0	0	0	0	0
20	52M	I	<1	0	63	+	0	0	+	0	0	0	0
21	56F	A	1	0	29	+	+	0	0	0	+	+	0
22	46M	I	27	0	70	0	+	+	+	+	+	+	+
23	62M	I	<1	VT	49	0	0	+	0	+	0	0	QM
24	56M	A	VT	VT	22	0	+	+	0	+	0	0	0
25	48F	A	<1	0	56	0	0	0	+	+	0	0	0
26	49M	A	2	VT	29	0	0	0	0	+	0	0	0
27	56M	A	18	Paired VPC	38	+	0	0	+	+	+	0	0

Summary of patient details including drug therapy at time of study.

A = anterior; ACE inhib. = angiotensin converting enzyme inhibitor; Antiarrhyth. = antiarrhythmic therapy; Beta Blocker = β-adrenergic antagonist; CA = calcium channel antagonist; Complex Vent. Ect. = presence of complex ventricular ectopy; Diur. = diuretics; DM = diabetes mellitus; I = inferior; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Nitr. = transdermal nitrates; P = procainamide; QM = quinidine and mexilitene; SH = systemic hypertension; VPCs = ventricular premature complexes; VPC/hr = frequency of ventricular premature complexes per hour; VT = ventricular tachycardia; 0 = absent or negative; + = positive or present.

disruption in regional cardiac adrenergic function is associated with the development of ventricular arrhythmias.

METHODS

The study consisted of 27 patients admitted to the coronary care unit at Parkland Memorial Hospital in Dallas, Texas, between June 1988 and April 1989; demographic details for these patients are summarized in Table I. All of these patients gave a history of prolonged chest pain at rest and had sequential electrocardiographic and enzyme changes consistent with AMI. The site of infarction was considered to be anterior if the electrocardiographic changes involved leads I, aVL, and precordial leads V_{1-6}, and inferior if the changes involved leads II, III and aVF. With use of these electrocardiographic criteria, 16 patients were considered to have sustained an inferior wall AMI (15 Q wave, 1 non-Q wave). All of these patients had perfusion abnormalities that involved the inferior or posterior, or both, aspects of the left ventricle. Eleven patients were considered to have anterior wall AMI (all Q wave) and each had perfusion abnormalities that involved the anterior or septal, or both, aspects of the left ventricle. Fifteen of the patients were men. Mean age of the patients was mean ± standard deviation 54 ± 9 years (range 37 to 71). Patients were studied a mean of 10 ± 4 days after AMI.

Radiopharmaceutical preparation: MIBG was radioiodinated by solid-phase exchange radioiodination by ammonium sulfate as described by Manger et al.[22] The I-123 used in these syntheses was produced by Xe-123 (p,2n) to C_s-123 to Xe-123 to I-123 and contained <0.1% radionuclide impurities at the time of calibration (Nordion, Ottawa, Canada).

Protocol: Before starting imaging, blood samples were obtained for serum catecholamine determinations. A heparin lock was inserted into a peripheral arm vein and the patients were asked to lie in a supine position for 30 to 40 minutes. From the heparin lock, blood was withdrawn into 10-ml heparinized vacutainers. The vacutainers were immediately immersed in an ice bath and centrifuged for 20 minutes at 2° to 4° centigrade and 1,000 ± 100 g. The serum was immediately separated and frozen for transportation. Plasma catecholamine analysis was performed using high-pressure liquid chromatography with electrochemical detection. After the blood specimens were obtained, the imaging protocol was begun.

Imaging protocol: One ml of Lugol's solution was given by mouth 30 to 60 minutes before injection. Then, 2.5 to 3.2 mCi of thallous chloride was injected intravenously with the patient in the upright position and imaging begun 10 minutes later. All imaging was performed using a dedicated 3-detector imaging system (PRISM 3000, Ohio Imaging, Bedford Heights, Ohio).

The detectors were constantly corrected for energy, uniformity, linearity and gain. The variability in the system sensitivity varies <0.5% in 24 hours. Projection images were acquired for 20 seconds each at 3° increments over 360° orbits and were recorded at a digital resolution of 64 × 64. Immediately after this acquisition, the patients were injected intravenously with 8 to 10 mCi of I-123 MIBG while in an upright position. Imaging was performed beginning at 15 minutes and repeated 4 (mean 4.0 ± 0.2) hours later. MIBG projection images were acquired for 20 seconds each at 3° increments over 360° orbits. Energy discrimination was provided by dual 20% windows centered over the 80 and 167 keV photopeaks of thallium (Tl)-201 and a 15% window centered over the 159 keV photopeak of I-123.

Image analysis: Transaxial tomographic sections from the Tl-201 and 15-minute and the 4-hour I-123 MIBG images, including the entire cardiac volume, were reconstructed by filtered backprojection of the projection images acquired over the 180° from the 45° right anterior oblique to 45° left posterior oblique positions. The filter used during reconstruction was the product of a ramp and Kaiser-Bessell filter (order of 5.0). Corresponding vertical long- and short-axis sections were selected from the reconstructed volumes. One representative vertical long-axis section and one apical, midventricular and basal short-axis section of the left ventricle were selected for analysis of segmental Tl-201 and I-123 MIBG activity. Particular care was taken to match the corresponding Tl-201 and I-123 MIBG sections to allow accurate comparisons between the 2 sets of images.

Images were analyzed semiquantitatively to provide a defect score. Each short-axis section was divided into 6 equally sized sectors for analysis. Only the apical portions of the vertical long-axis sections were considered. Two investigators (AIM, JRC) evaluated each image independently using a 3-point scoring scale (2 = absent or severely reduced, 1 = moderately or minimally reduced, 0 = normal activity). Disparities were resolved by consensus. Defect scores were calculated as the total score divided by the total possible score times 100%. The degree of mismatch between the Tl-201 and the 4-hour MIBG tomograms was obtained by expressing the differences between the defect scores as a percentage.

The reproducibility of this technique was evaluated by repeat analysis of the Tl-201 and MIBG tomographs in 5 patients, a total of 285 sectors. The degree of intraobserver and interobserver agreement in the scoring of the Tl-201 and MIBG tomograms was as follows: Tl-201 tomograms, 96 and 94%; MIBG tomograms, 83 and 89%. When disagreements occurred, they were usually a reflection of differences in the scoring of abnormal sectors, i.e., 0 or 1, rather than disagreements as to whether sectors were normal or abnormal.

I-123 MIBG tomograms were also analyzed quantitatively in the following manner: 3 regions of interest were generated, 1 in the infarct region, another in the zone bordering the infarct, and a third in a zone distant from the infarct region. The infarct region was placed in the most count-deficient area within the area of infarction, the bordering zone region was placed in the area where the mismatch between myocardial perfusion and late MIBG uptake was most obvious and the distant zone region was placed remote from the infarct in an area that had the highest count density. The zonal activities were expressed as mean counts per pixel per mCi corrected for decay and injected dose.

Predischarge left ventricular ejection fractions were calculated using gated equilibrium radionuclide ventriculography in 25 patients[23] and by contrast ventriculography in 1 patient.[24] Technically satisfactory predischarge Holter monitoring was performed in all but 2 patients a mean of 8.0 ± 4.8 days after infarction.

Statistical analyses: Results are expressed as mean ± 1 standard deviation. Nonparametric statistical tests were used because of the lack of normal distributions of the variables employed and the small number of patients in some of the groups analyzed. Wilcoxin's signed rank test and Mann-Whitney rank sum test were used for statistical comparisons of paired and unpaired data, respectively. Friedman's test was used to perform multiple comparisons between groups. The correlation between variables was performed using Spearman rank correlation estimates. A p value <0.05 was considered significant.

RESULTS

Iodine-123 MIBG and thallium-201 tomograms: Both the early (15-minute) and delayed images (4-hour) revealed evidence of regional abnormalities in MIBG uptake in the area of infarction. The location of the abnormalities in MIBG uptake corresponded to the location of Tl-201 perfusion abnormalities. The Tl-201 and early MIBG defect scores were similar, 23 ± 18 and 28 ± 28%, respectively. However, the defect scores from the 4-hour delayed MIBG tomograms were significantly greater (52 ± 22%) when compared with both the Tl-201 and early MIBG tomograms, p <0.001.

There was a wide variation in the degree of mismatch between the abnormalities observed in the Tl-201 perfusion and the delayed MIBG tomograms. The mean difference between the Tl-201 and the delayed MIBG defect scores was 26 ± 16% (range 3 to 63%). The degree of mismatch was related to the 4-hour MIBG defect score (r = 0.64, p <0.001), but was independent of the Tl-201 defect score. The discrepancy between perfusion and MIBG uptake occurred around the whole border of the infarct region.

Figures 1 and 2 show representative sets of images demonstrating the disparity between myocardial perfusion and MIBG uptake. Figure 1 is from a patient who had recently sustained an anterior AMI. The Tl-201 tomograms reveal a severe defect in the anteroseptal region. In comparison, the corresponding MIBG tomograms reveal a larger, more severe defect in the anteroseptal region which extends inferiorly to involve the inferior surface to the left ventricle. Figure 2 is from a patient with a recent inferior myocardial infarction. The Tl-201 images show an inferior perfusion abnormality which is most severe in the basal regions of the left ventricle. The early MIBG tomograms show a defect that

TABLE II Influence of Infarct Location on MIBG Defect Scores

Location of AMI	Early MIBG Defect Score	Late MIBG Defect Score	Thallium Defect Score	Late MIBG/ Tl Mismatch
Anterior (n = 11)	37 ±26	71 ±13	37 ±26	30 ±9
Inferior infarcts (n = 16)	14* ±11	39† ±17	19‡ ±14	21§ ±17

* $p = 0.008$; † $p = < 0.001$; ‡ $p = 0.005$; § $p = 0.16$.
Influence of infarct location on MIBG and Tl-201 defect scores.
All values expressed as mean ± standard deviation. See text for further details.
AMI = acute myocardial infarction; Anterior = anteriorly located infarcts; Early MIBG defect score = 15-minute defect score expressed as percent; Inferior = inferiorly located infarcts; Late MIBG defect score = 4-hour defect score expressed as percent; Late MIBG/Tl mismatch = mismatch between 4-hour MIBG defect and thallium-201 score expressed as percent; MIBG = I-123 meta-iodobenzylguanidine; Tl defect score = thallium-201 defect score expressed as percent.

is more extensive involving the midventricular and apical short-axis sections. The late MIBG defect is substantially larger, involving virtually the entire inferoposterior surface and extending to involve the contiguous inferoseptal and lateral aspects of the left ventricle.

Influence of the site of infarction: Patients who had sustained an anterior AMI had significantly greater Tl-201, and 15-minute and 4-hour MIBG defect scores than patients with inferior AMI; 37 ± 17% vs 19 ± 14%, $p = 0.005$; 37 ± 26% vs 14 ± 11%, $p = 0.008$; and 71 ± 13% vs 39 ± 17%, $p < 0.001$, respectively. The degree of mismatch between the Tl-201 and the delayed MIBG tomograms was also greater after anterior than inferior AMI, 30 ± 9% vs 21 ± 17%, $p = 0.016$ (see Table II).

Quantitation of four-hour regional MIBG myocardial uptake: The MIBG uptake in counts per pixel per mCi × 103 was 0.4 ± 0.3, 0.6 ± 0.3, and 0.9 ± 0.4 for 3 regions of interest, respectively ($p < 0.001$). The late MIBG uptake was significantly lower in all regions after anterior than inferior AMI; 0.3 ± 0.2 vs 0.5 ± 0.5 (infarct region), $p = 0.019$; 0.4 ± 0.4 vs 0.7 ± 0.4 (zone bordering the infarct), $p = 0.018$; and 0.7 ± 0.3 vs 1 ± 0.3 (zone distant from the infarct), $p = 0.014$.

Relation between regional abnormalities in four-hour MIBG uptake, left ventricular function and myocardial perfusion: A significant inverse correlation was found between the size of the 4-hour MIBG defect score and the predischarge left ventricular ejection fraction, $r = -0.73$, $p < 0.001$ (Figure 3). Despite the wide disparity observed between the Tl-201 and the 4-hour MIBG defect scores, a significant correlation was observed between these 2 variables, $r = 0.66$, $p < 0.001$ (see Figure 4).

Relation between ventricular arrhythmias in the late hospital phase and abnormalities in regional myocardial MIBG uptake: Significant ventricular ectopy was detected in 11 patients. Nine patients had evidence of >1 ventricular premature depolarization per hour, including 2 with paired ventricular premature complexes and 1 patient with ventricular tachycardia during predischarge 24-hour ambulatory monitoring. In addition, 2 patients had ≥1 episode of ventricular tachycardia detected during hospitalization despite <1 ventricular premature complex per hour on 24-hour electrocardio-

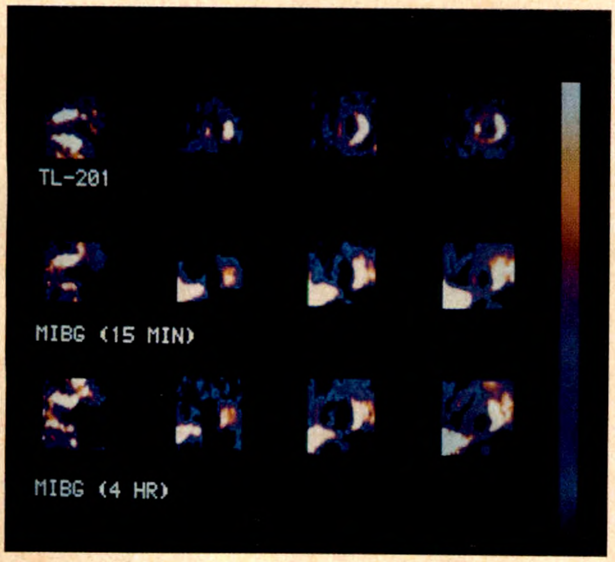

FIGURE 1. Representative sets of thallium-201 (Tl-201) and meta-iodobenzylguanidine (MIBG) tomograms from a patient who sustained a recent anterior myocardial infarction. *Top row* of images are the thallium-201 tomograms and the *middle* and *lower* tomograms are the 15-minute and 4-hour MIBG tomograms, respectively. The first column is a vertical long-axis section and the second, third and fourth columns are the apical, midventricular and basal ventricular short-axis sections, respectively.

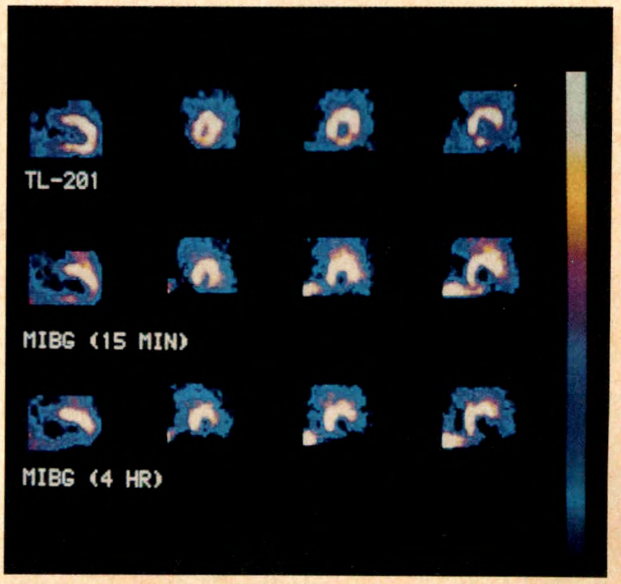

FIGURE 2. Images from a patient who recently sustained an inferior myocardial infarction. Abbreviations as in Figure 1.

graphic monitoring. Sixteen patients had no significant ventricular arrhythmia detected, of whom 14 had technically satisfactory predischarge 24-hour ambulatory electrocardiographic monitoring that revealed no evidence of complex ventricular ectopy or >1 ventricular premature complex per hour. The 4-hour MIBG defect scores were significantly higher in patients with evidence of ventricular arrhythmia than in patients with no evidence of ventricular arrhythmia, 63 ± 15% and 45 ± 23%, respectively, $p = 0.036$. No significant difference was observed between the Tl-201 perfusion defect score and the degree of mismatch between myocardial perfu-

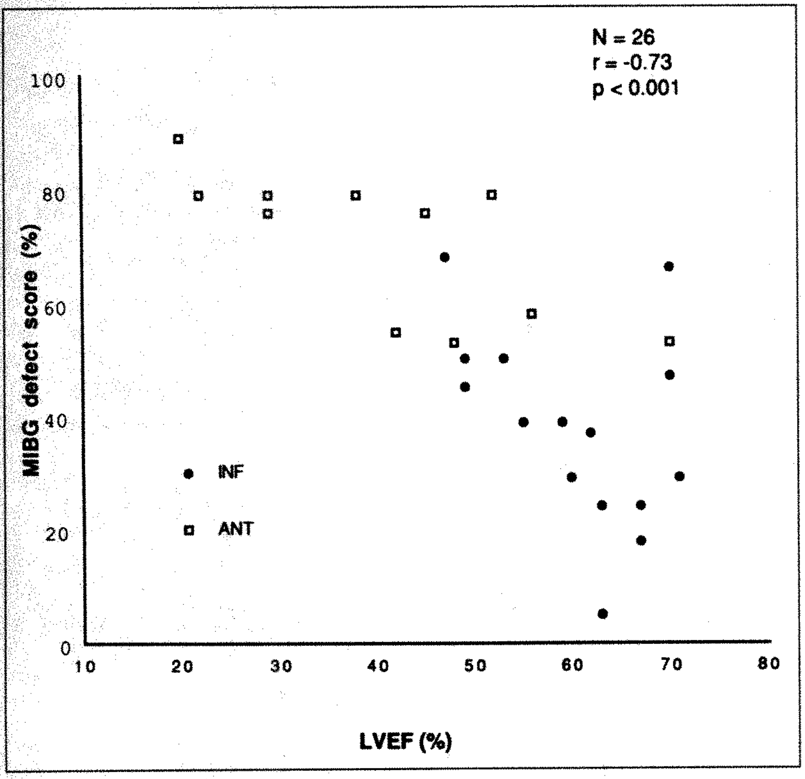

FIGURE 3. The relation between the 4-hour meta-iodobenzylguanidine (MIBG) defect scores and the predischarge left ventricular ejection fractions (LVEF) is shown. ANT = anterior; INF = inferior.

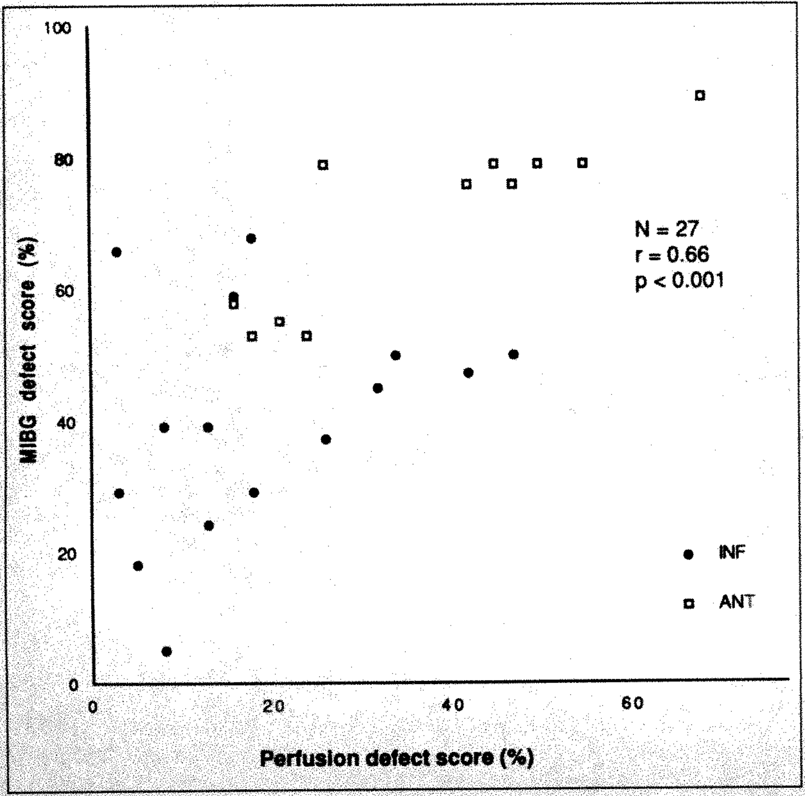

FIGURE 4. The relation between the 4-hour meta-iodobenzylguanidine (MIBG) defect scores and the thallium-201 defect scores is shown. Abbreviations as in Figure 3.

sion and the late MIBG defect scores in these 2 groups of patients, 31 ± 18% and 23 ± 18%, respectively.

Plasma catecholamine samples: The mean serum catecholamine level of the patients studied was 399 ± 259 pg/ml. There was a weak inverse correlation with the predischarge left ventricular ejection fraction, $r = -0.43$, $p = 0.027$. No significant correlation was observed between the serum catecholamine level and the MIBG defect score or MIBG uptake in the 3 regions of interest (infarct, border and distant zones).

Follow-up studies of MIBG uptake: Five patients underwent repeat study 6 ± 0.5 months after the initial study. At that time, all 5 patients still had abnormalities of MIBG uptake in the region of AMI. There was no difference between the follow-up and initial studies in the degree of mismatch between the thallium and 4-hour defect scores, 21 ± 12% and 23 ± 11%, respectively, difference not significant.

DISCUSSION

Principal findings: These results demonstrate that the effects of AMI on regional cardiac adrenergic function in humans can be evaluated noninvasively using single-photon emission computed tomography. We have also shown that the abnormalities in regional adrenergic function are more severe than the associated abnormalities in myocardial perfusion. In addition, we have observed that anterior AMI results in more severe disruption in adrenergic function than inferior AMI. Finally, the severity of the abnormality in regional adrenergic function correlates with the degree of left ventricular dysfunction and may be related to ventricular ectopy after AMI.

Experimental myocardial infarction has been shown to result in the disruption of sympathetic nerves as they run a course adjacent to the coronary arteries on the epicardial surface of the heart.[25,26] In addition, these studies have shown that the resulting area of sympathetic denervation is more extensive than the area of myocardial infarction. As a consequence, there is an area of noninfarcted myocardium that is denervated. This area of myocardium has been shown to have decreased catecholamine content, to be suprasensitive to infused catecholamines, and to have "denervation supersensitivity," which may provide a substrate for the genesis of ventricular arrhythmias.[21,27]

Dual imaging with radioiodinated MIBG and Tl-201 has been used to evaluate simultaneously the integrity of cardiac adrenergic function and myocardial perfusion in a canine model.[8,9] Minardo et al[8] showed that AMI results in MIBG defects that are more extensive than the corresponding Tl-201 defects. The presence of sympathetic denervation in the area of absent MIBG uptake was confirmed using neuroelectrophysiologic techniques.

Our results reveal a difference between the early and late distribution of MIBG. The early (15-minute) MIBG uptake, which has been previously suggested to reflect both neuronal and nonneuronal uptake, revealed defects that were smaller than the late (4-hour) MIBG uptake, which predominantly reflects neuronal uptake. Therefore, this implies the existence of a region around the border of the infarct that has different MIBG kinetics. The etiology of this remains speculative but may result from the presence of ischemic or stunned myocardium bordering the infarct zone where MIBG concentrates in a different manner than in the adjacent normal myocardium. Late (4-hour) MIBG uptake reflecting neuronal uptake revealed abnormalities that were more extensive than the associated abnormalities in myocardial perfusion. These findings are similar to those reported by Minardo et al.[8]

Relation with left ventricular function: Previous studies have demonstrated abnormalities in MIBG uptake in patients with ventricular dysfunction resulting from dilated cardiomyopathies.[6,7] Schoffer et al[7] showed a positive correlation between the myocardial concentration of norepinephrine and I-123 MIBG activity obtained from endomyocardial biopsy samples of patients with dilated cardiomyopathies.[7] Our results show a significant inverse correlation between the severity of the late MIBG defect score and the predischarge left ventricular ejection fraction. This may be explained in part by the size of the associated myocardial infarction since a similar relation was found between the left ventricular ejection fraction and the Tl-201 defect score. However, there was a significant inverse relation found between the predischarge left ventricular ejection fraction and absolute late MIBG uptake (counts per pixel per mCi) in the infarct, border and distant zones. This latter finding suggests that MIBG uptake, and consequently myocardial norepinephrine concentration in infarcted and noninfarcted myocardium may be related to the severity of left ventricular dysfunction after AMI.

Correlation with ventricular ectopy: One of the postulated mechanisms for the genesis of ventricular arrhythmias in patients with AMI is the disruption of adrenergic innervation of the heart. Experimental AMI has been shown to result in the disruption of efferent sympathetic nerves and denervation of an area of infarcted and contiguous noninfarcted myocardium. The area of noninfarcted denervated myocardium has been shown to develop denervation supersensitivity which may be arrhythmogenic.[21] The limited number of patients studied restricted the number of classifications that could be based upon the frequency and complexity of arrhythmias. The detection of complex ventricular ectopy (paired ventricular premature complexes or ventricular tachycardia) or the presence of a ventricular premature complex rate of ≥ 1 per hour during the late hospital phase after AMI has been shown by the Multicenter Post-Infarction Research Group to result in a significant increase in the 2-year mortality rate compared with patients with <1 ventricular premature complex per hour.[11] Therefore, we divided patients into 2 groups: those with no evidence of complex ventricular ectopy and a ventricular premature complex frequency of <1 ventricular premature complex per hour and those with complex ventricular ectopy and ≥ 1 ventricular premature complex per hour during the late hospitalization phase. Patients with evidence of significant ventricular ectopy had significantly higher mean late

MIBG defect scores than those without significant arrhythmia, despite no significant difference in the size of the Tl-201 perfusion defects in the 2 groups.

Follow-up studies: Follow-up studies were performed to determine whether any improvement occurred in regional cardiac adrenergic function which may have reflected sympathetic reinnervation. Follow-up studies were obtained in 5 patients, all of whom showed evidence of regional abnormalities 6 months after the index infarction. No significant change in the MIBG defect score or the degree of mismatch between myocardial perfusion and 4-hour MIBG defect scores was observed during this period.

Acknowledgment: We thank Jacob George, RTN, Anca Constantinesca, DSc, and Ray Josey, RTN, for their assistance in performing this study and Dorothy Gutekunst, Nancy Dickey and Chris Haverkorn for their help in the preparation of this manuscript.

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Insensitivity of Noninvasive Tests to Detect Coronary Artery Vasculopathy After Heart Transplant

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Obstructive coronary artery vasculopathy can be a major problem after cardiac transplant. The use of noninvasive tests to detect coronary artery vasculopathy was studied in 73 consecutive patients after heart transplant. Angiographically or autopsy-proved coronary artery disease was noted in 19 consecutive patients (26%) followed prospectively for 2.5 ± 1.3 years (mean ± standard deviation). Patients underwent yearly surveillance echocardiographic, rest/exercise–gated wall motion, oral dipyridamole thallium, ambulatory electrocardiographic monitor and angiographic studies. Positive test results were defined by decrease in ejection fraction, wall motion abnormality, failure to increase ejection fraction, lack of systolic blood pressure increase, and ischemic ST changes at maximal exercise (or on ambulatory monitor). Wall motion abnormalities and depressed ejection fraction on echocardiography were also abnormal studies as were fixed or reversible perfusion defects on thallium scan. Angiograms were considered positive when 50% luminal narrowing was observed and autopsy coronary artery vasculopathy was defined as cross-sectional coronary obstruction ≥70%.

No procedure that was examined proved to be a sensitive noninvasive detector of heart transplant coronary artery vasculopathy. All except ambulatory electrocardiographic monitoring had positive predictive values <50%. Interestingly, of the techniques evaluated, echocardiography was most sensitive (53%). The poor predictive ability of noninvasive testing in this population may be due to the fact that these tests are designed to detect effects of ischemia rather than coronary obstruction alone. Use of these particular noninvasive modalities routinely after heart transplant to detect coronary artery vasculopathy should be reconsidered because of their low sensitivity and predictive value when used as a surveillance screen.

(Am J Cardiol 1991;67:243–247)

Cardiac transplantation is now a common treatment for end-stage heart disease, and recent progress in immunosuppression has increased transplant recipient survival to 70% at 3 years.[1,2] Although the diagnosis and treatment of rejection and infection continues to improve, a substantial percentage of patients will die or require repeat cardiac transplantation because of coronary arteriopathy (coronary artery vasculopathy).[3-5] Gao et al[6] pointed out that the cumulative incidence of coronary artery vasculopathy was well over one-third of their total heart transplant population. Despite recognition of this problem, there remains incomplete understanding of its pathophysiology. Transplant vasculopathy is clearly different from native coronary vessel arteriosclerosis. Whereas allografts may show focal obstruction quite similar to native vessel disease, the majority of transplant coronary artery vasculopathy is a diffuse, concentric narrowing affecting the large epicardial and small endocardial arteries.[7] This difference creates unique challenges.

The accuracy of noninvasive tests in detecting coronary artery vasculopathy after cardiac transplantation has not been completely characterized. Reports on the use of thallium scintigraphy in patients who have had heart transplants are conflicting.[8,9] To assess critically the usefulness of some of the more commonly available noninvasive predictors of coronary artery vasculopathy, we examined 73 consecutive patients who had undergone orthotopic cardiac transplantation utilizing coronary angiography and a spectrum of noninvasive tests. This study was specifically designed to evaluate the predictive value of these tests in detecting heart transplant coronary artery vasculopathy.

METHODS

Patient group: This study prospectively followed 73 consecutive orthotopic cardiac transplant patients receiving new hearts between April 1984 and August 1989 (Table I). There were 65 men and 8 women (mean age ± standard deviation, 47 ± 14 years). Mean follow-up time was 2.5 ± 1.3 years. These patients were examined in both a cross-sectional and longitudinal fashion for the development of coronary artery vasculopathy. In addition, patients were followed for rejection episodes. The patients underwent, on an annual basis, 2-dimensional echocardiography, gated radionuclide wall motion assessment at rest and exercise, oral dipyridamole thallium-201 single-photon emission computed tomography and 48-hour Holter monitoring for arrhythmia and silent ischemia. The patients, as part of a

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From the Multi-Organ Transplant Center of the Methodist Hospital and Baylor College of Medicine, Houston, Texas. This study was supported, in part, by the Cullen Trust for Health Care, Houston, Texas. The computational assistance was provided by the CLINFO Project, and funded by Grant RR-0035, Division of Research Resources, National Institutes of Health, Bethesda, Maryland. Manuscript received July 12, 1990; revised manuscript received and accepted September 24, 1990.

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routine follow-up, also underwent selective coronary arteriography on an annual basis. Three groups were excluded from this study: those not surviving 3 months, those not undergoing coronary angiography, and those not having autopsy in the event of death.

Patients received a standard immunosuppressive protocol, previously described, that included azathioprine, prednisone and cyclosporine.[10] Monoclonal antibody therapy (OKT3) was not routinely used as induction prophylaxis in the early postoperative period. Rejection episodes were treated with an ad hoc protocol common to most heart transplant centers.

Cardiac catheterization: Annual diagnostic left-sided cardiac catheterization with selective coronary arteriography was routinely performed as previously mentioned. Some patients, because of symptoms possibly related to coronary artery vasculopathy, had more frequent catheterization, and patients who had transplantation after June 1988 (n = 7) underwent a 6-week posttransplant catheterization for baseline documentation of coronary artery status. The cineangiograms were all recorded with similar catheter sizes, magnification and views, and were analyzed by 2 independent cardiologists who were unaware of the patients' clinical status. In the event of a discrepancy between the 2 interpreters, a third cardiologist reviewed the films, again in a masked fashion, and the patients were placed in a group with 2 agreeing votes. The patients were said to have coronary artery vasculopathy if any vessel had a >50% luminal narrowing by visual assessment. The diagnosis of this disease by arteriography is problematic. The cutoff of 50% was chosen so that the diagnosis could be made with relative certainty by visual assessment.

Two-dimensional echocardiography and Doppler imaging were performed with a standard Hewlett Packard model 77020A diagnostic echocardiogram using a 2.5-MHz transducer. All patients were studied in the left lateral recumbent position using multiple views through the parasternal and apical windows. The views selected for ejection fraction measurement were parasternal long axis, apical 2 chamber and apical long axis. Ejection fractions were measured at end diastole and end systole and calculated on an off-line computer and quantitative program (Digisonics, Houston, Texas). All images analyzed were of technical quality adequate to assess wall motion and ejection fraction and the method for quantitation has been substantiated by our laboratory. An echocardiogram was considered abnormal and indicative of ischemic disease if there was a reduction in ejection fraction from the postoperative baseline without evidence of rejection or if any wall motion abnormality was present. Echocardiography, when regional wall motion abnormalities are present, has been shown to be 95% sensitive for detecting coronary occlusion in patients with suspected myocardial infarction.[11,12]

Gated radionuclide wall motion angiograms were obtained using 30 mCi of technetium 99-m injected through a peripheral vein. A single-crystal gamma camera with an all purpose collimator was used. The camera's energy discrimination was set at 140 keV with a 20% window. Images were obtained in the anterior, 70° and 45° left anterior oblique positions. The image with best septal delineation was chosen for analysis. After the resting images were obtained, the patients underwent supine bicycle exercise starting at 200 kpm for 180 seconds per stage with doubling of work load at each 3-minute stage. A study was considered abnormal if: (1) rejection could not be documented and there was a decrease in left ventricular ejection fraction from a previous gated wall motion study; (2) with exercise, the patient developed a new wall motion abnormality; (3) there was a decrease in ejection fraction during exercise; or (4) there were any wall motion abnormalities, either global or segmental, were noted on a resting study that had not been noted previously and remained unchanged during the exercise state. This study in the patient without transplantation has proved useful in detecting the severity of coronary artery disease.[13]

Ambulatory electrocardiographic monitoring was obtained over 48 hours using 2 sequential 24-hour ambulatory monitors with event recorders (Delmar model 419), and these recordings were then analyzed on a Delmar 7 Inovator computer-assisted electrocardiographic analyzer. Any abnormalities noted by the scanning technologist were double checked by a cardiologist again unaware of the patient's clinical status. Ambulatory monitor recordings were analyzed for bradycardia or tachyarrhythmias, frequent ventricular premature complexes or the presence of ST-segment changes. A positive study was one in which any horizontal ST change >1.5 mm occurred or nonsustained ventricular tachycardia was noted (≥3 beats), or any bradycardia <40 beats/min were recorded. This test was used to detect silent or manifest myocardial ischemia. In patients with native coronary artery disease similar ST-segment changes indicate ischemia.[14–17]

Exercise electrocardiograms were obtained during the gated wall motion exercise study. These were done on a supine bicycle ergometer using a standard protocol of stepwise increase in work beginning at 200 kpm and increasing by 200 kpm with each stage. During exercise the patient's blood pressure was monitored every 2 minutes and the patient had constant electrocardiographic monitoring throughout the exercise period. An abnormal study was considered one in which a decrease in systolic blood pressure or failure of systolic blood pressure to increase with exercise by 10% was noted. The exercise test was also considered positive if any ST abnormality consistent with ischemia was present.

The final diagnostic test performed was a dipyridamole thallium perfusion study. Patients were given 300 mg of oral dipyridamole in a suspension. The use of 400 mg of dipyridamole has been shown to be as good a predictor as maximal exercise thallium or intravenous dipyridamole.[18] We used 300 mg of dipyridamole in our laboratory to avoid the excessive adverse effects seen with 400 mg. The patients were then monitored closely for any adverse effect and for any significant electrocardiographic or hemodynamic change after the oral dose. At 45 minutes after the dose of dipyridamole, 3 mCi of

TABLE I Noninvasive Coronary Artery Vasculopathy Detection Study: Demographics

Variables	All Pts.	CAV (n = 19)	No CAV (n = 54)	p Value
Recipient age	47 ± 14	44 ± 14	48 ± 14	NS
Donor age	27 ± 9	25 ± 7	27 ± 9	NS
Days alive	927 ± 481	916 ± 511	931 ± 474	NS
Ischemic time	156 ± 72	150 ± 76	158 ± 71	NS
Recipient gender				
Men	65 (89%)	15 (79%)	50 (93%)	0.1
Women	8 (11%)	4 (21%)	4 (7%)	
Donor gender				
Men	59 (81%)	14 (74%)	45 (83%)	NS
Women	14 (19%)	5 (26%)	9 (17%)	
CHF etiology				
CAD	40 (55%)	12 (63%)	28 (52%)	NS
IDC	26 (35%)	6 (32%)	20 (37%)	
Valvular	5 (7%)	1 (5%)	4 (7%)	
Other	2 (3%)		2 (4%)	

CAD = coronary artery disease; CAV = coronary artery vasculopathy; CHF = congestive heart failure; IDC = idiopathic dilated cardiomyopathy; NS = not significant (p >0.05).

TABLE II Noninvasive Coronary Artery Vasculopathy Detection Study: Patient Studies

Study	No. of Pts. with ≥1 Study	No. of Pts. with No Studies
Gated wall motion	58 (79%)	15 (21%)
Echocardiogram	73 (100%)	
24-hour ambulatory ECG (Holter)	59 (81%)	14 (19%)
Oral dipyridamole thallium	57 (78%)	16 (22%)
Supine bicycle exercise	58 (79%)	15 (21%)

Forty-five of 73 patients underwent all 4 studies.
ECG = electrocardiography.

thallium-201 was injected intravenously and flushed with saline solution. Imaging was obtained with a single crystal rotating gamma camera (ADAC ARC 3000-3300) with a high-resolution parallel-hole collimator. The image was obtained over a 180° acquisition arc. Tomographic slices were then reoriented in the standard horizontal long, vertical long and short axes for visual and quantitative analysis. In addition, quantitation was done using a 2-dimensional polar map of myocardial radionuclide activity. The map was generated based on pixel count activity of each short-axis slice, and the polar map of each patient statistically compared with a normal data bank as previously reported by our laboratory.[19] The test was considered abnormal if there was a visual or quantitative (>3% on polar map) perfusion defect either fixed or with reperfusion. If a defect was present, patients underwent 4-hour and occasionally 24-hour reperfusion imaging. This test has been shown to be a sensitive predictor of coronary obstruction >50%.[20] Oral dipyridamole was used because this preparation was available and approved for use, and in our laboratory at a dose of 300 mg, it had an 89% sensitivity for detecting lesions in patients without myocardial infarction.[21]

All noninvasive tests were interpreted by observers unaware of the clinical status of the patients, particularly of angiographic results. Autopsy examination of hearts from deceased transplant patients were examined in standard fashion with particular attention paid to the epicardial coronary arteries. Coronary artery vasculopathy was considered present if focal or diffuse obstruction of >75% cross-sectional diameter was observed.

Statistical analysis: Data were analyzed using the computing capabilities of the CLINFO data analysis system. Standard descriptive statistics characterized the groups. Continuous variables were compared with *t* tests. Descriminating variables were compared using chi-square or Fisher's exact test. Sensitivity, specificity, positive and negative predictive values for any noninvasive test used angiographic or autopsy evidence of coronary artery vasculopathy as the reference positive standard. These values were determined using standard formulas: sensitivity = true positive/true positive + false negative; specificity = true negative/true negative + false positive; positive predictive value = true positive/true positive + false positive; negative predictive value = true negative/false negative + true negative.

RESULTS

Based on angiogrpahic and autopsy data, the patients were classified into 2 separate groups, those with (n = 19) and those without (n = 54) angiographic coronary artery vasculopathy. Results of the demographic analysis are summarized in Table I. The 2 groups were compared to determine any differences. No statistical difference was noted between the groups with and without coronary artery vasculopathy regarding recipient age, donor age, donor ischemic time or the etiology of the recipient's native heart disease. The sex of the recipients showed a trend toward more women in the coronary artery vasculopathy group. This may relate to the hypothesis that coronary artery vasculopathy is an immune-mediated phenomenon and young women have higher levels of rejection.[22] This trend, however, did not attain statistical significance, possibly because during this time few women underwent cardiac transplantation. Additionally, endomyocardial biopsy scores did not correlate with the presence or absence of coronary artery vasculopathy in a representative subset of these patients as previously described.[23] No difference was noted in immunosuppressive treatment protocol between the 2 groups.

Each noninvasive indicator of coronary artery vasculopathy was tested separately. Patients had variable numbers of each test due to the longitudinal nature of this study (Table II). Some patients may not have had a particular study for various reasons. Of the 73 patients studied, 45 had all 5 tests at least once; 15 patients had no gated wall study, 14 patients had no Holter and 16 patients had no persantine thallium. The total number of tests done in each category included 966 echocardiograms, 99 Holters, 174 gated wall motion studies, 170 exercise tests and 103 thallium scans.

A test was considered positive if any component of that test was abnormal. Abnormal gated wall motion study results were seen in 7 of 15 patients with coronary

TABLE III Predictive Value of Noninvasive Tests for Coronary Artery Vasculopathy After Heart Transplant*

Study	Sensitivity (%)	Specificity (%)	Predictive Values Positive (%)	Predictive Values Negative (%)
GWM	46	78	32	78
Holter	56	81	53	83
Echo	58	69	39	82
Exercise	21	77	21	77
Thallium	21	88	33	77

* Seventy-three orthotopic transplant patients between February 1984 and January 1988.
Echo = echocardiogram; Exercise = supine bicycle exercise test; GWM = gated wall motion study; Holter = 24-hour ambulatory electrocardiogram; Thallium = oral dipyridamole thallium test.

TABLE IV Number and Estimated Cost of Noninvasive Studies

Study	CAV	No CAV	Total Studies	Test Cost	Total Cost
Thallium	28	75	103	$1,070	$110,210
Perfusion	3	6			
GWM	52	122	174	$931	$161,994
Wall abn	8	18			
Ex EF	5	18			
Ex BP	3	5			
Holter	27	72	99	$518	$51,282
Any arrhythmia	8	12			
Tachycardia only	7	11			
Bradycardia only	1	1			
Echocardiography	278	688	966	$443	$427,938
Wall abn	14	22			
Echo <50%	13	22			
Total cost					$751,424

BP = blood pressure; EF = ejection fraction; Perfusion = perfusion defect on thallium scan; Wall abn = abnormal wall motion present; other abbreviations as in Tables I and III.

artery vasculopathy (47%) compared with 15 of 43 patients without coronary artery vasculopathy (35%) (difference not significant [NS]). Results of the exercise study were similar: 11 of 43 tests in patients without coronary artery vasculopathy were positive (26%) vs 3 of 15 in the group with coronary artery vasculopathy (20%) (p = NS). Single-photon emission computed tomography dipyridamole thallium imaging showed that 6 of 43 patients without (14%) and 3 of 14 patients with (21%) coronary artery vasculopathy had a positive study (p = NS). Echocardiographic wall motion abnormalities or depressed ejection fraction were more frequent in the group with coronary artery vasculopathy (11 of 19 [58%] vs 17 of 54 [31%] patients without coronary artery vasculopathy) but this was of marginal significance ($p = 0.039$). The most striking difference was seen with ambulatory monitoring, where detection of any arrhythmia was significantly more frequent in the group with coronary artery vasculopathy: 9 of 16 (56%) compared with 8 of 43 (19%) in the group without coronary artery vasculopathy ($p < 0.01$). However, ambulatory monitoring analyzed for ST shifts showed no significant difference.

The sensitivity, specificity, positive and negative predictive values of each of the noninvasive tests examined are depicted in Table III. The positive predictive value for coronary artery vasculopathy of a Holter test showing arrhythmia was 53%, and of an echocardiogram with an ejection fraction <50% was 39%. The specificity and negative predictive values of all tests, however, were high (>75%), but because of low sensitivity and positive predictive value, these studies are not good screening tools for detecting the presence of coronary artery vasculopathy. The positive predictive value is particularly interesting, the highest being ambulatory monitoring (53%) and the lowest, exercise testing (21%). These predictive values are no better than chance in selecting patients with coronary artery vasculopathy.

Table IV lists the total number of tests done. Because many patients had serial studies at annual follow-up visits, the number of tests was substantially higher than the number of patients followed. This table also demonstrates the significant cost incurred by performing these studies. Estimated expense if these tests were done today would be over $750,000 and their results would have little effect on the ability to predict which patient had asymptomatic coronary artery vasculopathy.

DISCUSSION

Transplant coronary artery vasculopathy may be the factor limiting long-term survival of heart transplant recipients, and attention has focused on the detection and pathophysiology of this disease. Unfortunately, our ability to noninvasively detect coronary artery vasculopathy after heart transplant was compromised by the insensitivity of the tests performed. Specificity, on the other hand, was high. However, this group of patients was followed a relatively short period of time (mean follow-up 30 months) and these tests generally were performed as routine surveillance studies rather than to address patients' unexplained symptoms. Currently, noninvasive methods of coronary artery vasculopathy detection assess effects of ischemia and have been demonstrated as sensitive predictors of atheosclerosis in nontransplant patients. However, since coronary angiography can define anatomic changes, this test and the noninvasive studies sometimes do not agree. Anatomic narrowing can be present in the transplant patient without ischemia and, conversely, ischemia may manifest in patients with small vessel coronary artery vasculopathy undetectable by angiography. The diffuse nature of this disease may result in balanced ischemia that would be difficult to detect by an imaging method that detects regional myocardial differences. Other types of noninvasive surveillance testing such as radionuclide myocardial perfusion imaging, in the presence of maximal exercise to induce ischemia, may be a more sensitive coronary artery vasculopathy indicator. We are currently prospectively evaluating the utility of maximal stress thallium scintigraphy in asymptomatic heart transplant patients.

Data presented here suggests that, until a sensitive noninvasive screening test for coronary artery vasculopathy after cardiac transplantation is identified, these patients should undergo routine surveillance coronary angiography at regular intervals.

The routine use of noninvasive screening tests for coronary artery vasculopathy after cardiac transplantation described in this report should be reconsidered because of test insensitivity, patient inconvenience and cost. It is essential to identify other noninvasive procedures that might supplant angiography to detect this problem. However, it is unknown if these tests, or any others, will have prognostic significance in determining which patients with coronary artery vasculopathy progress to retransplantation or death. For example, a positive noninvasive study predicting cardiac ischemia may have powerful prognostic value despite its insensitivity when used as a screening tool. Finally, the use of noninvasive testing in patients with inexplicable symptoms possibly related to ischemic heart disease may still be a valuable clinical tool in the management of heart transplant patients.

Acknowledgment: We express appreciation to Barbara Bond for her secretarial skills and editorial expertise.

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Comparative Effects of Overweight on Cardiovascular Risk in Younger Versus Older Men

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The relation of age and body mass index (BMI) to atherosclerosis risk factors was examined in 357 men. Older (≥45 years) men had higher ($p < 0.01$) systolic and diastolic blood pressures, fasting cholesterol and glucose, and 1-hour glucose and insulin levels. Fasting insulin and triglyceride levels were not significantly different between the 2 age groups. Although older men ($n = 170$) had greater values for several risk factors, overweight (BMI >25.5 kg/m^2) increased risk factors more in men younger than 45 years ($n = 187$). In younger men, those with higher BMIs had a greater prevalence, respectively, of blood pressure >140/90 mm Hg (35.2 vs 11.2%, $p < 0.0001$), cholesterol >200 mg/dl (53.5 vs 29.3%, $p < 0.001$), fasting triglycerides >150 mg/dl (38.0 vs 10.3%, $p < 0.0001$), 1-hour glucose >160 mg/dl (15.5 vs 5.2%, $p < 0.05$), fasting insulin >11 μU/ml (28.2 vs 5.2%, $p < 0.0001$), and 1-hour insulin >110 μU/ml (28.2 vs 9.5%, $p < 0.001$). In contrast, among older men, the prevalence of elevated blood pressure, cholesterol, triglycerides and glucose values was not significantly greater in the subgroup with high BMI. However, elevations of fasting (19.6 vs 6.4%, $p < 0.05$) and 1-hour insulin (29.3 vs 11.5%, $p < 0.01$) values were more common among older men with higher BMIs. Data indicate that older men have greater values for several cardiovascular risk factors than do younger men. Overweight increases the prevalence of cardiovascular risk factors more in younger men.

(Am J Cardiol 1991;67:248–252)

Overweight is a risk factor for hypertension,[1] cardiovascular disease[2] and premature death.[3] The risk associated with overweight is not uniformly distributed. For example, overweight increases the risk of cardiovascular disease[2] and premature death[4] more in younger men. These observations may be partially explained by data indicating that overweight increases the prevalence of hypertension more in younger men.[5] However, to our knowledge, differential effects of overweight on the prevalence of other risk factors in these 2 groups are unknown. Age-related differences in the effects of overweight on cardiovascular risk factor profiles in men could have important implications for disease prevention. Consequently, we reviewed our risk factor data in men to assess the relation of age to the cardiovascular risk of overweight.

METHODS

Patients: Data were obtained on 378 men self-referred to our Atherosclerosis Risk Factor Detection Clinic. Most of the subjects participating in this screening process learned about the clinic through newspaper bulletins or from acquaintances familiar with the program.

Measurements: Height and weight were obtained on lightly clothed subjects without shoes. Body mass index (BMI) was calculated,[6] and casual (seated) blood pressure was measured by mercury sphygmomanometry. Diastolic blood pressure was determined by phase IV of the Korotkoff sounds. Heart rate was quantified by palpation of the radial pulse. Blood samples were drawn in the fasting state for plasma cholesterol,[7] triglycerides,[7] immunoreactive insulin[8] and whole blood glucose.[9] Subjects then drank 100 g of glucose in 10 ounces of water over the next 5 minutes. A 1-hour blood sample was obtained for measurement of whole blood glucose and plasma insulin. In 8 patients studied on or after March 6, 1986, blood glucose was measured in serum[10] rather than in whole blood. Glucose values from the last 8 persons were converted to whole blood glucose by the formula: whole blood glucose = (serum glucose − 6)/1.15.[11]

Top normal values (mean + 2 standard deviations [SD]) for fasting and 1-hour insulin were obtained in a subgroup seen in the Atherosclerosis Risk Factor Detection Clinic. These 48 subjects (35 men and 13 women) were (1) within ±10% of ideal body weight, (2) nonsmokers, (3) physically fit according to self-report of moderate to vigorous exercise, (4) normotensive, (5) normolipidemic, and (6) normoglycemic.[11] No subject

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had a history of hypertension, gout, hyperlipidemia, diabetes, and renal or cardiovascular disease. These subjects had mean fasting insulin values of 4.3 μU/ml (mean + 2 SD = 10.5) and 1-hour insulin of 43.2 μU/ml (mean + 2 SD = 110.3). Therefore, 11 and 110 were selected as top normal fasting and 1-hour insulin values, respectively. Our values for fasting and 1-hour postglucose (100 g) insulin levels concur with those obtained by Bjorntorp et al[12] in physically fit, non-overweight men who were 54 to 56 years old.

Statistical analysis: Twenty-one men with fasting glucose >150 mg/dl or 1-hour glucose >250 mg/dl or a history of diabetes, or any combination of these, were eliminated from the analysis, since the insulinemic response of moderate and severe diabetic patients to an increase in glucose is significantly impaired.[13] Thus, the final study group consisted of 357 men. Differences between the 2 subgroups of men demarcated by age < vs ≥45 years were assessed by Student's *t* test. The effect of BMI < vs ≥25.5 kg/m^2 within each subgroup on the prevalence of selected risk factors was examined with chi-square analysis. The triglyceride data were not normally distributed.[14] The triglyceride values were logarithmically transformed to normalize the distribution. Data analyses were conducted using established statistical programs.[15]

TABLE I Descriptive Variables for Men Stratified by Age < or ≥ 45 Years Old

Age Stratification	<45 (n = 187)	≥45 (n = 170)	p Value
Age (years)	32.4 ± 0.5	55.6 ± 0.6	<0.00001
BMI (kg/m^2)	25.4 ± 0.3	26.0 ± 0.2	NS
Systolic BP (mm Hg)	121 ± 1	130 ± 1	<0.0001
Diastolic BP (mm Hg)	81 ± 1	84 ± 1	<0.04
HR (beats/min)	72 ± 1	73 ± 1	NS
fIRI (μU/ml)	5.9 ± 0.4	6.1 ± 0.4	NS
1-hour IRI (μU/ml)	68 ± 4	85 ± 4	0.002
TG (mg/dl)	126 ± 8	135 ± 7	NS (log)
fWBG (mg/dl)	91 ± 1	95 ± 1	<0.01
1-hour WBG (mg/dl)	115 ± 2	142 ± 3	<0.0001
TC (mg/dl)	190 ± 3	211 ± 3	<0.0001

BMI = body mass index; BP = blood pressure; f = fasting; HR = heart rate; IRI = plasma immunoreactive insulin; NS = not significant (p >0.05); TC = total plasma cholesterol; TG = fasting plasma triglycerides; WBG = whole blood glucose.

RESULTS

Descriptive variables (mean ± standard error of the mean) for the 2 groups of men stratified by age < vs ≥45 years are listed in Table I. The age limit was adapted from the Australian Heart Foundation Study which observed a stronger relation between overweight and prevalence of hypertension in men <45 years versus other age and gender subgroups.[5] Older men had greater values than younger men for several risk factors. Table II presents data on men within each age group demarcated by BMI <25.5 vs ≥25.5 kg/m^2. Overweight tended to cause larger increases of risk factor levels in younger men.

Table III displays the percentage of men in 4 subgroups stratified by age < or ≥45 years and BMI < or ≥25.5 kg/m^2 whose values exceeded generally accepted top normal levels for the risk factors measured. The BMI cutpoint was also adapted from the Australian Heart Foundation Study which observed a sharp increase in the prevalence of hypertension among men <45 years whose BMI exceeded this value.[4] A BMI of 25.5 kg/m^2 corresponds to a Metropolitan Relative Weight of 109 to 113% according to the 1959 Tables.[16]

The risk factor prevalence data in Table III are based on the following:

1. BLOOD PRESSURE: Systemic hypertension was defined as casual blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or both (Korotkoff phase IV).
2. CHOLESTEROL: Cholesterol values ≥200 mg/dl were defined as elevated based on National Cholesterol Education Program guidelines.[17]
3. TRIGLYCERIDES: Triglycerides >150 mg/dl were considered abnormal, since decreased high-density cholesterol values are frequent in persons with triglyceride concentrations exceeding that level.[18]
4. FASTING AND ONE-HOUR WHOLE BLOOD GLUCOSE: The upper normal limits for fasting and 1-hour glucose are based on the Fajans-Conn criteria.[11]
5. FASTING AND ONE-HOUR INSULIN: Normal limits for fasting and 1-hour insulin values are defined in Methods.

Younger (<45 years) overweight men (BMI ≥25.5 kg/m^2) had a significantly higher prevalence for mea-

TABLE II Effect of Overweight on Selected Risk Factors in Younger and Older Men

	Men <45 Years			Men ≥45 Years		
	<25.5 kg/m^2 (n = 116)	≥25.5 kg/m^2 (n = 71)	p Value	<25.5 kg/m^2 (n = 78)	≥25.5 kg/m^2 (n = 92)	p Value
BMI (kg/m^2)	23.0 ± 0.2	29.3 ± 0.4	≤0.0001	23.4 ± 0.2	28.2 ± 0.2	≤0.0001
Systolic BP	119 ± 1	126 ± 2	≤0.002	130 ± 2	130 ± 2	NS
Diastolic BP	78 ± 1	86 ± 1	≤0.0001	83 ± 1	84 ± 1	NS
HR (beats/min)	71 ± 1	73 ± 1	NS	72 ± 1	73 ± 1	NS
fIRI (μU/ml)	4.2 ± 0.3	8.6 ± 0.8	≤0.0001	4.7 ± 0.4	7.4 ± 0.6	≤0.0002
1-hour IRI (μU/ml)	53 ± 3	93 ± 7	≤0.0001	69 ± 5	98 ± 6	≤0.0003
fWBG (mg/dl)	88 ± 1	96 ± 2	≤0.0001	94 ± 1	95 ± 13	NS
1-hour WBG (mg/dl)	106 ± 3	129 ± 4	≤0.0001	142 ± 4	143 ± 4	NS
TG (mg/dl)	97 ± 4	172 ± 17	≤0.0001	137 ± 13	134 ± 7	NS
TC (mg/dl)	184 ± 3	200 ± 4	≤0.001	209 ± 4	213 ± 4	NS

Abbreviations as in Table I.

TABLE III Prevalence (%) of Selected Atherosclerosis Risk Factors in Men Stratified by Age and Body Mass Index

	<45 Years		≥45 Years	
BMI (kg/m²) Risk Factor	<25.5 (n = 116)	≥25.5 (n = 71)	<25.5 (n = 78)	≥25.5 (n = 92)
Htn	11	35****	44	41
	1.7†	1.4	13	11
TC	29	54***	55	65
	0.0‡	1.4	2.6	5.4
TG	10	38****	28	30
fWBG	1.7	5.6	2.6	3.3
1-hour WBG	5.2	15.5*	18	24
fIRI	5.2	28****	6.4	20*
1-hour IRI	9.5	28***	11.5	29**

p value ≤ * 0.05; ** 0.01, *** 0.001, **** 0.0001 by chi-square.
† Percent taking antihypertensive medications.
‡ Percent taking hypolipidemic medications.
Htn = hypertension; other abbreviations as in Table I.

sured risk factor variables, except fasting glucose, than leaner men of similar age (Table III). Older men manifested smaller BMI-related increases in the prevalence of risk factors. Figure 1, which is based on data in Table III, shows the excess and relative risks of overweight for selected risk factors separately for younger and older men.

DISCUSSION

Differences in risk factor values between younger and older men: Men ≥45 years old had higher values than younger men for several risk factors including systolic and diastolic blood pressure, fasting cholesterol and glucose, and 1-hour glucose and insulin.[19,20] However, other risk factors including BMI,[21] heart rate[22] and fasting triglyceride[23] insulin levels[24] were not significantly different between the 2 groups (Table I).

Influence of overweight on risk factor values within each age group: Overweight younger men had significantly greater values for measured risk factor variables except heart rate (Table II). The effect of overweight was generally less among older men (Tables II and III and Figure 1). Overweight younger men have a cardiovascular risk factor profile (Table III) comparable to older men who are at the greatest absolute risk of cardiovascular disease.[2]

Blood pressure: Overweight (BMI >25.5 kg/m²) was associated with a threefold higher prevalence of hypertension in younger men. In contrast, overweight was

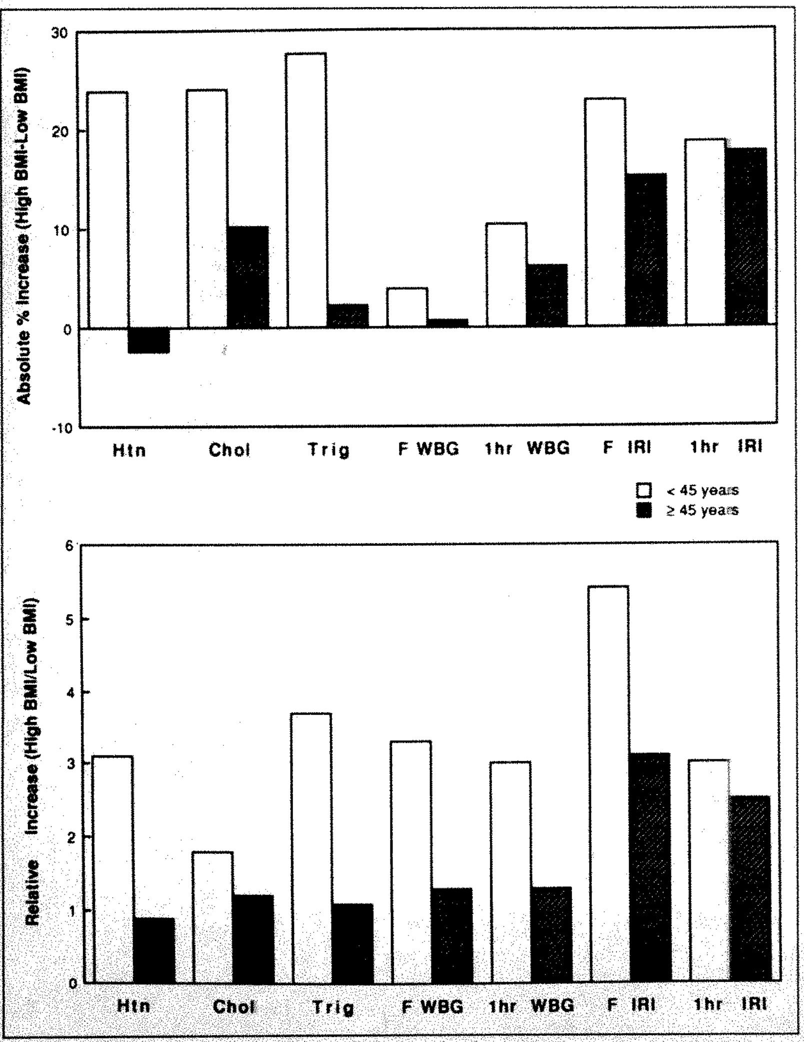

FIGURE 1. Effect of body mass index (BMI) on the excess *(top panel)* and relative *(bottom panel)* risk for selected cardiovascular risk factors in men stratified by age. Chol = cholesterol; F = fasting; Htn = hypertension; IRI = plasma immunoreactive insulin; TRIG = triglycerides; WBG = whole blood glucose.

not associated with a significantly greater prevalence of hypertension in our sample of men >45 years. These data are similar to the findings of the Australian Heart Foundation study[5] which reported a stronger relation of weight to hypertension in men <45 years old compared with other age and gender subgroups. Nevertheless, overweight may increase the risk of heart failure in both younger and older hypertensive subjects by imposing a dual burden of elevated preload on a heart working against a higher afterload.[25]

Insulin: An association between weight, insulin and hypertension was reported.[26] Insulin levels, per se, are an unlikely explanation for the stronger association between overweight and hypertension in younger men, since overweight increased the prevalence of fasting and 1-hour hyperinsulinemia in both age groups (Table III, Figure 1). However, insulin induces greater neurogenic activation in men <40 vs men >60 years old.[27] These findings could contribute to the greater plasma norepinephrine and vascular α-adrenergic tone in overweight versus leaner young men.[28] Consequently, differences of insulin action rather than insulin concentration may explain greater effects of overweight on blood pressure in younger versus older men.

Glucose: Older men had higher values for fasting and 1-hour glucose despite higher 1-hour insulin values (Table I). This suggests that insulin resistance contributes to an age-related decline of glucose tolerance in our subjects. The prevalence of fasting hyperglycemia was sufficiently low in all subgroups to the extent that no significant differences were observed. However, the age-corrected prevalence of 1-hour hyperglycemia[11] was significantly increased by overweight only in younger men. However, as noted previously, overweight was associated with an increase in 1-hour hyperinsulinemia in both younger and older men (Table III, Figure 1). These data suggest that overweight is associated with greater resistance to insulin's effects on glucose disposal or suppressing gluconeogenesis, or both, in younger men.

Triglycerides: Younger men had a larger BMI-related increase in the prevalence and relative risk of hypertriglyceridemia (Table III, Figure 1). However, insulin normally suppresses hepatic very low density lipoprotein production.[29] Thus, a greater weight-related hepatic resistance to insulin in younger men may explain our triglyceride data.

Cholesterol: Cholesterol levels were higher in older men (Table I). Overweight significantly increased the prevalence of cholesterol values >200 mg/dl only in younger men. The absence of a significant effect of overweight on cholesterol values in men 50 to 79 years old was documented previously.[30] Although the cause for these age-related differences is unknown, greater effects of overweight on α-adrenergic tone in younger men could partially explain these observations.[31]

Limitations of this cross-sectional study and comparisons to previous epidemiologic investigations: These data were obtained on self-referred men who may not reflect health characteristics of the general male population. Since we observed age-related differences in the association between weight and several cardiovascular risk factors, comparison of BMI values in our subjects with larger samples of U.S. men is of particular interest. The mean ± SD BMI values for men aged 30 to 39 and 50 to 62 years in the National Health and Nutrition Survey II were 25.6 ± 4.0 and 26.2 ± 3.9 kg/m^2, respectively.[32] These BMI values are very similar to those for the younger and older men in this study (25.4 ± 4.0 and 26.0 ± 2.6 kg/m^2, respectively).

The results from our study are consistent in other respects with observations from larger surveys. First, in the Australian Study,[5] the strongest relation between weight and blood pressure was observed in men aged <45 years. Second, the relatively minimal differences in cholesterol between overweight and leaner elderly men were also noted previously.[30] Third, whereas older men have higher values than younger men for several risk factors, our data (Table II) are consistent with reports that overweight has greater adverse health effects in younger men.[2,4,5] In fact, increased cardiovascular risk for younger men begins at mild levels of overweight.[2,5] Because the mean BMI for men of this age group (Table I) lies at the margin of increased risk, large numbers of younger men are affected.[32]

This study did not address potential explanations for the greater risk of overweight in younger versus older men. The lower apparent risk of overweight in older men may reflect premature mortality in younger men with high-risk obesity.[4,32] Another possibility is that older men with BMIs <25.5 kg/m^2 may have sufficient adiposity (replacing lean mass) to raise their risk factors.

Our data extend previous observations by showing that overweight is associated with a significant increase in prevalence not only of elevated blood pressure but also of cholesterol, triglycerides and 1-hour glucose in younger men. The relative risk of overweight for each of these variables appears to be less in older men. Overweight is associated with significant elevations of fasting and 1-hour hyperinsulinemia in both age groups. However, our interpretation of the data suggests that overweight influences insulin action more adversely in younger men.

Acknowledgment: We are grateful for the expert assistance of Maria Borondy in examining many of the subjects seen in the Atherosclerosis Risk Factor Detection Clinic; Mary Frescura in preparing the manuscript; Janet Kniffen, Luciana Yu and Mark McGinnis in performing laboratory assays; and Jill Kneisley and Nicholas Schork for the data analyses. Portions of this work were presented at the Forty-fifth Annual Meeting of the Midwest Section, AFCR, Chicago, Illinois (Clin Res 35:847A: 1987).

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Immediate and Short-Term Results of a 1988–1989 Coronary Angioplasty Registry

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To determine the relevance of recent refinements in angioplasty technology to our particular practice, the records of 507 consecutive patients undergoing a first percutaneous transluminal coronary angioplasty (PTCA) at our center between October 1988 and May 1989 were reviewed. At the time of PTCA, 41% of these patients had class IV angina and 44% were identified as having multivessel disease. Dilatation was attempted in 734 lesions (mean 1.5 per patient), of which 95 (13%) were chronic total occlusions. Overall, 69% of the 734 lesions were judged anatomically complex, and, in dilating these lesions, a rail-type device was used almost exclusively. Successful dilatation was achieved in 659 of the 734 (90%) attempted lesions. There were low incidences of the major complications of death (0.4%), myocardial infarction (1.8%) and emergency bypass surgery (1.8%). Acute rethrombosis occurred in 54 patients (11%). In these patients, initial strategy of repeat dilatation was successful in 38 of 47 patients (81%). Overall, primary clinical success at PTCA was achieved in 480 patients (95%). At a mean follow-up of 7.5 ± 1.5 months in 497 of the study patients, the event-free rate (freedom from cardiac death, myocardial infarction, repeat PTCA or coronary bypass surgery or recurrence of severe [class III to IV] angina) was 71%. In conclusion, despite the often complex coronary disease in patients currently presenting to our center, a high initial success rate and acceptable short-term outcome of PTCA was achieved.

(Am J Cardiol 1991;67:253–258)

When coronary angioplasty using the original nonsteerable system was introduced, the primary success rate of the procedure was low and many anatomic restraints limited its application.[1] However, over the last decade, innovative balloon catheter technology has eliminated most of these anatomic limitations and, as a consequence, expanded the indications for percutaneous transluminal coronary angioplasty (PTCA).[2,3] In addition, this technologic progress along with increasing operator experience has gradually improved the primary success rate.[2,3]

The present report assesses the immediate and 6-month follow-up results obtained in a large consecutive series of patients undergoing their first PTCA in the period 1988 to 1989 and makes mention of the use in our practice of one particular advance in PTCA "hardware," the rail-type dilatation system.[4]

METHODS

Study group: Between October 1988 and May 1989, 647 consecutive patients underwent PTCA at our center. Angioplasty was never attempted in the acute phase of myocardial infarction. In 140 patients, the procedure was performed after an earlier PTCA; this group was excluded from further analysis. Accordingly, the study population comprised 507 patients who underwent a PTCA for the first time.

Procedure: Angioplasty was performed by way of either the brachial or the femoral approach. After the control angiogram was obtained, either a Hartzler Micro™ dilatation catheter (Advanced Cardiovascular Systems, Mountain View, California) or a rail-type dilatation system was chosen. A common strategy was followed in all procedures. The Micro catheter was used for so-called "classic" lesions,[5] which are easy to cross and have a low risk of dissection. In all other cases, a bare 0.014-inch floppy guidewire was used to cross stenoses, whereas occlusions were tackled with the stiffer 0.014-inch standard wire (Advanced Cardiovascular Systems). Then, either a Piccolino® (Schneider Shiley, Zürich, Switzerland) or an RX® (Advanced Cardiovascular Systems) balloon catheter was advanced over the guidewire. At the end of the procedure, the balloon catheter was removed with the guidewire kept in place, at least until control angiograms had shown a satisfactory result.

In-hospital management: After the PTCA procedure, patients continued to receive intravenous heparin, 1,000 IU/hour for 24 hours. Calcium antagonists and 100 mg of aspirin were routinely prescribed. If a patient

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TABLE I Patient Demographics (n = 507)

Age (yr)	59 ± 9[†]
Male/female	3.3/1
Systemic arterial hypertension[*] (%)	30
Cigarette smokers and ex-smokers (%)	72
Diabetes mellitus[*] (%)	9
Serum total cholesterol (mg %)	246 ± 50[†]

[*] Defined as necessitating medical treatment.
[†] Mean ± standard deviation.

developed signs or symptoms of recurrent ischemia, repeat coronary angiography and repeat PTCA, using a rail-type dilatating system, were performed (except in patients with large dissections who were sent directly to surgery). Patients in whom repeat PTCA was unsuccessful either underwent urgent bypass surgery or, when the myocardium at risk was judged to be small, were treated conservatively in the cardiac intensive care unit.

Patient follow-up: After hospital discharge, repeat coronary angiography was only performed if judged to be clinically indicated. As a routine, every patient was scheduled for an outpatient visit and functional testing ≥6 months after PTCA. Follow-up data were obtained from clinical records and physician mail or telephone questionnaire.

Definitions: Coronary lesions were visually estimated in 2 perpendicular views and expressed as the percentage of diameter reduction compared with the diameter of the nearest "normal" arterial segment. A lesion was considered significant when the mean value of the 2 views was ≥50%. A vessel was considered diseased when at least 1 such lesion was present. Using these criteria, patients were classified as having either single or multivessel disease. Lesions were classified as either complex or classic, the latter description being applied to so-called type A lesions.[5] Primary angiographic success at PTCA was defined as a reduction in luminal narrowing by ≥20% to a residual narrowing of <50%. Primary clinical success was defined as the successful dilatation of the culprit lesions without the occurrence of death, myocardial infarction or emergency coronary bypass surgery during hospitalization. Intimal dissection was defined as an intimal flap with a double lumen contour extending beyond the site of the lesion. Acute rethrombosis was defined as an intracoronary filling defect that compromised the vessel patency by >50%. Untoward events during the in-hospital period were defined as death, cerebrovascular accident, coronary artery surgery, repeat PTCA and myocardial infarction. Repeat PTCA was defined as an attempt to reopen the previously dilated artery after acute rethrombosis had occurred outside the catheterization laboratory. Thus, repeat dilatations for filling defects during the original PTCA attempt were not included under this definition. Myocardial infarction was defined as a typical change in cardiac enzymes (>2 times the upper normal limits of creatine kinase or an MB fraction >4%, or both). At control angiography, restenosis was defined as ≥50% coronary narrowing at the site of prior dilatation. Similarly, progression of disease was defined as a stenosis of ≥50% in a nondilated segment that was not present at the time of the original PTCA. During a short-term follow-up of 6 months, occurrence of death, repeat PTCA, coronary bypass surgery or nonfatal myocardial infarction, were counted as untoward events.

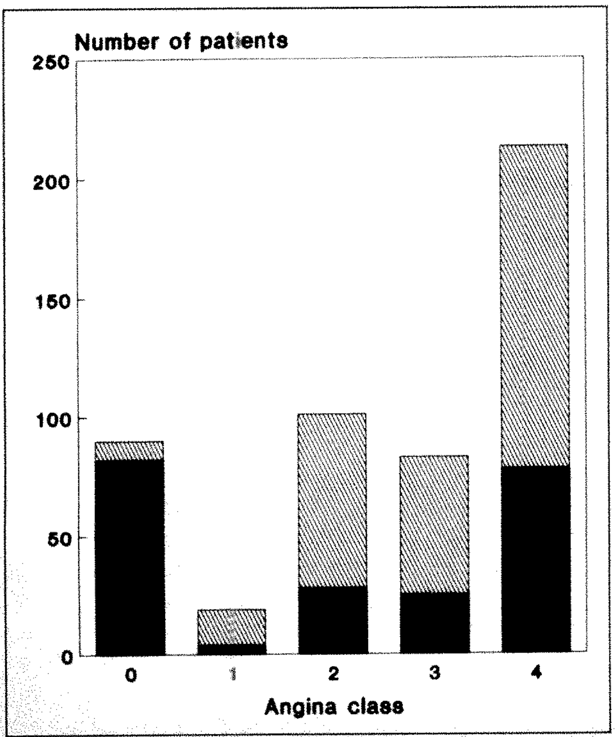

FIGURE 1. Distribution of patients according to anginal status (Canadian Cardiovascular Society classification). ***Black bars,*** **number of patients with a previous myocardial infarction.**

Data collection: All relevant clinical and angiographic data have been entered into a computer-based registry, the details of which have been reported elsewhere.[6] These data were recorded at the beginning and the end of the hospital stay and during the 6-month follow-up period.

Statistical analysis: Data are expressed as mean ± standard deviation. Intergroup analysis was performed using SAS, a commercially available computer program. A p value <0.05 was considered significant.

RESULTS

Baseline characteristics: Patient demographics are given in Table I. In Figure 1 the symptomatic status and the number of patients with previous myocardial infarction are depicted. Previous myocardial infarction was present in 221 patients (44%); 41% of them were treated with thrombolytic agents. Angina at rest was present in 42% of the study patients. Although 18% of the patients were asymptomatic at the time of PTCA, almost all (92%) had experienced a previous myocardial infarction. The average number of diseased vessels was 1.5. One-, 2- and 3-native vessel disease was present in 56, 34 and 6% of the patients, respectively; 4% had undergone previous bypass surgery (all these patients had multivessel disease). In all, 958 lesions were identified in the 507 study patients. The mean number of lesions per patient was 1.9.

TABLE II Strategy of PTCA According to Number of Diseased Vessels

	Vessel Disease (%)				
	1-Vessel (n = 285)	2-Vessel (n = 173)	3-Vessel (n = 29)	Postoperative (%) (n = 20)	Total (%) (n = 507)
≥2 lesions attempted	19	63	66	30	37
Arteries attempted					
Right	28	11	10	—	20
LAD	51	13	17	15	35
LC	21	18	31	30	21
Right + LAD	—	18	4	—	6
Right + LC	—	18	7	10	7
LAD + LC	—	22	14	5	8
Right + LAD + LC	—	—	17	—	1
Left main	—	—	—	5	1
Bypass graft	—	—	—	35	1

LAD = left anterior descending artery; LC = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; Right = right coronary artery.

Acute outcome at percutaneous transluminal coronary angioplasty: Angioplasty was performed using the brachial approach in 60% and the femoral approach in 40% of the patients. The Hartzler Micro was used in 31% of the lesions and a rail-type system was preferred in 66%.

In the 507 patients, dilatation of 734 lesions in 659 vessels was attempted. The major reasons that the 224 lesions were not attempted were: (1) presence of a chronic total occlusion not supplying an area of viable myocardium; (2) luminal narrowing ≤60%; and (3) lesion location on a secondary branch not supplying an appreciable area of viable myocardium. Primary clinical success was achieved in 480 of these 507 patients (95%). However, lesion success rate was only 90%, mainly due to failure to cross chronic occlusions in patients with multivessel disease. Of the 734 attempted lesions, 506 (69%) were classified as type B or C.[5] Included in this group were 95 total occlusions, representing 13% of all lesions attempted. Of the total 734 attempted lesions, 57 (8%) could not be crossed with either the guidewire or the balloon. These 57 lesions comprised 21 high-grade complex stenoses and 36 total occlusions. In addition, the final angiographic result was not considered satisfactory in 18 lesions (2%). Complete revascularization was achieved in 295 patients (58%). The strategy of PTCA was examined separately for each type of native vessel disease, as well as for postoperative patients (Table II).

Acute rethrombosis during the procedure was observed in 35 patients (7%), 26 with stenoses and 9 with total occlusions. This complication was treated by repeat inflations in 31 patients, with success in 25 (81%). Repeat inflations were more frequent in patients with multivessel disease than in 1-vessel disease (20 vs 11, $p = 0.07$) and in patients having multilesion rather than single lesion dilatation (18 vs 13, $p = 0.02$). Two of the 31 patients initially treated with repeat inflations finally needed emergency surgery, and 4 sustained a myocardial infarction. In 4 patients, repeat inflations were not performed: 1 was referred directly to surgery and 3 were treated medically without evidence of myocardial infarction.

Dissection occurred in 38 patients (7%). In 6 patients this event was complicated by abrupt occlusion and these patients were considered as having acute rethrombosis. Two patients underwent emergency bypass surgery and 1 was referred to the coronary care unit with a limited myocardial infarction. Proximal dissection of the left main stem by the guiding catheter occurred in 1 patient who had elective surgery. Occlusion of a major side branch led to a myocardial infarction in 1 patient.

Postprocedural in-hospital events: After the PTCA was performed, acute rethrombosis occurred in 19 patients (4%). This complication was observed during heparin infusion in 18 patients, and after the heparin infusion had been stopped in only 1 patient. Two patients, both with serious hemodynamic problems, were referred directly to surgery. In 1 patient the acute rethrombosis was treated medically. In the remaining 16 patients, urgent repeat PTCA was performed, which was successful in 13 (81%). Of the 3 patients in whom repeat PTCA was unsuccessful, 1 underwent emergency bypass surgery and the other 2 had evidence of only limited ischemia and were treated conservatively. In-hospital death occurred in 2 patients. One patient died after emergency surgery. The other patient, on chronic hemodialysis, died from a noncardiac disorder.

A comparison of all major in-hospital events for patients with single versus multivessel disease and for patients with single versus multilesion dilatation is given in Table III. In addition, 1 patient developed a subdural hematoma during heparin treatment.

Follow-up results: Patients discharged from the hospital having achieved primary success (480) or partial clinical success (17) at initial PTCA were followed up at our center for a minimum of 6 months; 100% follow-up was achieved. Diagnostic coronary angiography was performed in 152 patients (31%) (Table IV). Restenosis was considered the mechanism responsible for recurrence of ischemia in 113 of these patients (74%). In 7, the responsible mechanism was thought to be ischemia originating from lesions left undilated at initial PTCA, and, in 5 patients (3%), disease progression was thought to be the responsible process. Overall, repeat PTCA was

TABLE III Number of Major In-Hospital Events (%)

	Vessel Disease			
	1-Vessel (n = 285)	Multivessel (n = 222)	p Value	All Pts. (n = 507)
Death	1 (0.3)	1 (0.4)	NS	2 (0.4)
AMI	8 (2.8)	1 (0.4)	NS	9 (1.8)
CABG	3 (1.0)	6 (2.7)	0.03	9 (1.8)
Repeat PTCA	14 (4.9)	2 (0.9)	0.02	16 (3.1)
All	26 (9.0)	10 (4.4)	0.07	36 (7.1)
	Lesion Dilation			
	Single Lesion (n = 318)	Multilesion (n = 189)		
Death	1 (0.3)	1 (0.5)	NS	2 (0.4)
AMI	5 (1.6)	4 (2.1)	NS	9 (1.8)
CABG	4 (1.3)	5 (2.6)	NS	9 (1.8)
Repeat PTCA	13 (4.1)	3 (1.6)	NS	16 (3.1)
All	23 (7.3)	13 (6.8)	NS	36 (7.1)

AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

performed in 106 patients (21%) and 4 patients needed repeat dilatation for acute rethrombosis. In 17 patients (3%) coronary bypass surgery was preferred. During the follow-up period there were 2 cardiac and 2 noncardiac deaths. Event rates were not significantly different when patients with single versus multivessel disease or single versus multiple lesion dilatation were compared, except for an excess in coronary bypass surgery in the multilesion dilatation group (Table V). The overall event-free (freedom from cardiac death, nonfatal myocardial infarction, need for repeat PTCA or coronary surgery, recurrence of class III or IV angina) rate at 6 months in these patients was 71%.

DISCUSSION

This study examines the immediate outcome of 507 consecutive patients undergoing a first PTCA in an 8-month period, October 1988 to May 1989, and traces the 6-month outcome in 497 of these patients. Although there is a plethora of publications detailing the outcome after PTCA of various populations of patients with coronary artery disease, it is the current nature of this study that makes it of particular interest and relevance. Accordingly, this study shows what can be achieved when experienced operators, using the most current dilatation strategies, take advantage of the most up-to-date PTCA "hardware" (such as the rail-type dilatation system). In our study, angiographic success was achieved in 90% of all the attempted lesions and clinical success was achieved in 95% of the patients. (This observation of a clinical success rate in excess of the angiographic success rate is explained by the not altogether infrequent scenario in our study where, in the same patient, the "culprit lesion" was successfully dilated together with an unsuccessful dilatation attempt of a chronic total occlusion). The immediate results of PTCA in our study become even more encouraging when one considers the clinical and angiographic characteristics of our study population. Of these 507 patients, 42% had angina at rest, 44% had experienced a previous myocardial infarction and 44% were identified as having multivessel disease. Furthermore, of all attempted lesions in our study, a relatively high percentage (13%) were chronic occlusions.

A particular feature of our study was the use of the rail-type dilatation system (used in 66% of the lesions). This system, first described in 1986, and only gaining widespread use in experienced centers in the last few years, has a number of important technical advantages.[4] This technique allows all steps of the PTCA procedure to be monitored with (1) high-quality angiograms; (2) easy, rapid and safe recrossing and redilation of the stenosis if necessary; and (3) stepwise dilatation of the stenosis with repeated use of bigger balloons without need for extension wires, advisable in complex anatomic situations. Favorable immediate results with use of the rail-type system have also been reported recently by de Feyter et al.[7] A particular consideration is that in our series, the rail-type system was not used in dilatation of so-called classic lesions (lesions that are easy to cross and have a low risk of dissection).[5] Instead, the technique tended to be reserved for more complex lesions. This observation further emphasizes the important likely contribution of this technique toward the favorable immediate results.

In our patient population, there were gratifying low rates of occurrence of 3 major acute complications of PTCA: death, need for emergency bypass surgery and myocardial infarction (0.4, 1.8 and 1.8%, respectively). These results compare favorably with those reported by the National Heart, Lung, and Blood Institute Registry (1.0, 3.4 and 4.3%, respectively) concerning 1,802 patients undergoing their first PTCA during 1985 to 1986.[8] In contrast to our study patients, a somewhat greater number of Registry patients were identified as

TABLE IV Etiology of 152 Clinical Problems During Follow-Up

	Etiology				
Clinical Problem	Restenosis	Nondilated Lesion	Progression of Disease	Nonsignificant Findings	Total
Recurrent chest pain	91	6	4	21	122
Silent ischemia	15	1	1	6	23
Myocardial infarction	7	0	0	0	7
Total (%)	113 (74)	7 (5)	5 (3)	27 (18)	152

TABLE V Number of Major Follow-Up Events (%)

	Vessel Disease			
	1-Vessel (n = 281)	Multivessel (n = 216)	p Value	All Pts. (n = 497)
Death	3 (1.1)	1 (0.5)	NS	4 (0.8)
AMI	6 (2.1)	6 (2.8)	NS	12 (2.4)
CABG	9 (3.2)	8 (3.7)	NS	17 (3.4)
Repeat PTCA	62 (22.1)	48 (22.2)	NS	110 (22.1)
All	80 (28.5)	63 (29.2)	NS	143 (28.7)
	Lesion dilation			
	Single Lesion (n = 313)	Multilesion (n = 184)		
Death	2 (0.6)	2 (1.1)	NS	4 (0.8)
MI	5 (1.6)	7 (3.8)	NS	12 (2.4)
CABG	6 (1.9)	11 (5.9)	0.03	17 (3.4)
Repeat PTCA	68 (21.7)	42 (22.8)	NS	110 (22.1)
All	81 (25.8)	62 (33.6)	0.08	143 (28.7)

Abbreviations as in Table III.

having multivessel disease (53 vs 44% in our study population). Similarly, the mean number of diseased vessels (1.8) and lesions (2.5) was slightly greater than in our series (1.5 and 1.9, respectively). However the mean number of attempted vessels (1.3) and lesions (1.5) in our series were quite similar to those reported in the Registry (1.3 and 1.6, respectively).

The observations made in the present study regarding the complication of abrupt reocclusion are of interest. The incidence of this complication in our series (11%) does not differ significantly from earlier reports.[9-11] This observation tends to support the suggestion that the rate of acute rethrombosis and dissection does not change with operator experience, but rather that factors intrinsic to the procedure and the lesions may be operative. An important feature of our study is that, in most of these patients with acute rethrombotic occlusion, an initial strategy of attempting to redilate the lesion was successful in 38 patients (81%). Our strategy of attempting repeat PTCA rather than sending the patient to surgery (as was often done in other centers with patients having a low threshold) was prompted by the results of recent studies suggesting the efficacy of such a strategy.[12,13] It is likely that the use of the rail-type system also contributed to the high success rate in the treatment of acute rethrombosis by repeat PTCA.

The frequency of in-hospital events was very similar in patients with single and multivessel disease. Furthermore, when patients were classified according to whether they had single lesion or multilesion PTCA, the frequency of in-hospital events was again similar. These observations may, at first glance, appear somewhat surprising but become less so when one considers our data more carefully. When a thrombotic event occurs in a patient with multivessel rather than 1-vessel disease, the treatment of choice is most probably surgery. The lower rate of repeat PTCA in patients with multivessel disease is further explained by the longer duration of the procedure; more patients in this subgroup had repeat balloon inflations during the procedure itself which, as previously stated, were not counted as events.

At a mean follow-up of 7.5 months, 354 of the 497 patients (71%) who had a successful or partially successful result at initial PTCA remained free of major cardiac events. Because of the adverse clinical and anatomic features in many of our study patients, the short-term results achieved with PTCA in these patients should be regarded in a favorable light. Moreover, a large body of evidence suggests that, once patients get past the 6-month restenosis "time window," there is a very low subsequent annual rate of adverse events.[14-16] Our results also serve to reinforce the general wisdom that the major factor undermining the short- to medium-term success of PTCA is the unyielding high restenosis rate.[2,3,15,16] In our study, restenosis appeared to be the responsible mechanism for the occurrence of the great majority (74%) of adverse clinical events at follow-up (Table IV). In contrast to the high clinical restenosis rate (23%) seen in our study, the disease progression rate (1%) was low. These observations are in accordance with general observations regarding restenosis and disease progression after PTCA.[2,3,16] An interesting feature of our study was that in only 7 patients (1.4%) was the occurrence of adverse events judged to be the result of ischemia originating from lesions not dilated at initial PTCA. This suggests that, although a significant number of our study patients (41%) had incomplete revascularization at PTCA, this degree of revascularization (dilating the culprit lesions only) is often adequate.[14]

Study implications: It is likely that our experience of increasing numbers of patients with advanced and complex coronary disease currently presenting for PTCA mirrors the experiences of many other centers. Despite the considerable challenge posed by patients such as those described in our study, high initial success rates and favorable short- to intermediate-term outcome may be achieved. A particular feature of our study is the useful role of the rail-type system in the dilatation of complex lesions and in the treatment of acute rethrombosis.

Acknowledgment: We are indebted to Sabine Van Roey and Marianne Potargent for expert manuscript preparation and Stef Renkens for technical and programming assistance.

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Sustained Reduction in Valvular Regurgitation and Atrial Volumes with Tailored Vasodilator Therapy in Advanced Congestive Heart Failure Secondary to Dilated (Ischemic or Idiopathic) Cardiomyopathy

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Afterload reduction therapy can acutely improve hemodynamic function in patients with advanced heart failure; however, it is unknown if initial reductions in mitral and tricuspid regurgitation and atrial volumes can be sustained with oral therapy. Atrial volumes and atrioventricular valve regurgitation were measured using 2-dimensional and Doppler echocardiography with color-flow imaging in 14 patients with dilated heart failure (ejection fraction 17 ± 4%) before and after 3 ± 1 days of intensive vasodilator and diuretic therapy tailored to hemodynamic goals. Echocardiography was repeated again after 6 ± 2 months on oral vasodilators and a flexible diuretic regimen. Acute therapy reduced systemic vascular resistance from 1,760 ± 460 to 1,010 ± 310 dynes·s·cm^{-5}, pulmonary artery wedge pressure from 30 ± 5 to 17 ± 4 mm Hg, and right atrial pressure from 13 ± 5 to 7 ± 3 mm Hg, and led to a 61% increase in stroke volume (from 36 ± 10 to 58 ± 14 ml) ($p < 0.01$). Mitral and tricuspid regurgitation, determined by color-flow fraction, initially decreased from 0.34 ± 0.17 to 0.20 ± 0.20 and from 0.33 ± 0.15 to 0.13 ± 0.13, respectively ($p < 0.001$). This reduction was sustained at 6 months. Significant decreases occurred with acute therapy, with further reductions at 6 months in both mean left atrial volume (from 100 ± 25 to 80 ± 19 to 65 ± 15 cm^3) and right atrial volume (from 85 ± 23 to 64 ± 23 to 52 ± 14 cm^3) ($p < 0.001$). Echocardiographic estimate of mean pulmonary artery pressure decreased acutely (from 42 ± 5 to 30 ± 7 mm Hg, $p < 0.001$), then remained unchanged at follow-up. Congestive symptoms and signs were also markedly improved at 6 months ($p < 0.05$). In conjunction with clinical improvement in 6-month survivors with advanced heart failure, acute reductions in atrial volumes and atrioventricular valve regurgitation can be sustained on long-term oral vasodilators and diuretics.

(Am J Cardiol 1991;67:259–263)

Vasodilator therapy acutely improves hemodynamic function in patients with low-output congestive heart failure,[1,2] but the contribution of initial improvement to a sustained response has been questioned. We demonstrated in patients with advanced heart failure that acute, intensive vasodilator and diuretic therapy tailored to hemodynamic goals causes significant reductions in mitral and tricuspid regurgitation and atrial volumes, thereby decreasing the "atrial overload" contributing to congestive symptoms.[3] It is not known, however, if these acute improvements can be sustained with oral therapy in an outpatient setting. Using 2-dimensional and Doppler echocardiography with color-flow imaging, we measured the initial reductions in atrioventricular regurgitation and atrial volumes and sought to determine if these improvements were sustained on long-term, tailored therapy with vasodilators and diuretics.

METHODS

Study patients: We enrolled 28 consecutive patients admitted to our coronary care unit for evaluation and treatment of advanced heart failure (New York Heart Association functional class III or IV), all of whom underwent echocardiography before and after 3 ± 1 days of therapy tailored to hemodynamic goals. All patients were in sinus rhythm and none had primary valvular disease. The group in this study comprises the 14 patients who could be studied a third time after ≥3 months (13 men and 1 woman, mean age ± standard deviation 52 ± 10 years). Heart failure was attributed to coronary artery disease in 5 patients and to idiopathic dilated cardiomyopathy in 9. Within 6 months of referral, 8 of the 14 patients not studied died (3 from heart failure before hospital discharge and 5 suddenly at home), 4 underwent cardiac transplantation (3 electively, waiting as outpatients, and 1 urgently), 1 had coronary artery bypass surgery and 1 was lost to follow-up.

At the time of admission, the severity of heart failure was estimated for each patient on the basis of symptoms (orthopnea and gastrointestinal symptoms of an-

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orexia, early satiety, and nausea on a 0 to 4 scale of increasing severity as described previously[4]) and physical examination. Elevated jugular venous pressure, rales, ascites and edema were also each graded on a 0 to 4 scale by a cardiologist unaware of the echocardiographic findings.

Echocardiographic techniques: Baseline 2-dimensional echocardiography with pulsed Doppler and color-flow imaging (Hewlett Packard no. 77020A) was performed on each patient within 2 hours of insertion of a pulmonary artery flotation catheter. Mitral and tricuspid regurgitation were assessed in 3 ways, as previously detailed[3,5,6]: (1) visual estimate of the percentage of the atrium covered by color-flow evidence of the maximal regurgitant jet in the apical 2- and 4-chamber views (4-chamber view only for tricuspid regurgitation), graded on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe); (2) color-flow fraction: planimetered area of maximal regurgitant jet area divided by planimetered area of the atrium (average of the 2- and 4-chamber view values for mitral regurgitation); and (3) velocity-volume index: the color-flow fraction multiplied by the atrial volume (see below), to compensate for potential changes in atrial volume with therapy. Color-flow Doppler imaging data were not available for 1 patient.

Left and right atrial volumes were calculated using Simpson's Rule from the average of 2 on-line planimetered areas in the apical 2- and 4-chamber views (4-chamber view only for the right atrial volume).[7]

An estimate of the mean pulmonary artery pressure was made from the acceleration time of the pulsed Doppler tracing in the right ventricular outflow tract, using the previously validated formula[8]: mean pulmonary artery pressure = 73 − (0.42 × acceleration time).

All tracings were performed by 1 investigator blinded to the sequence of studies and clinical status of the patients.

Design of therapy: After completion of the baseline echocardiogram, hemodynamic measurements were obtained in the postabsorptive state, including triplicate cardiac output measurements using the thermodilution technique. Intravenous nitroprusside and diuretics were then administered, tailored to approach systemic vascular resistance $\leq$1,200 dynes·s·cm^{-5}, pulmonary artery wedge pressure $\leq$15 mm Hg and right atrial pressure $\leq$8 mm Hg, as previously described.[9] When optimal hemodynamic functions were achieved, oral captopril, enalapril, or oral hydralazine and nitrates were added as the nitroprusside was tapered. Oral vasodilator doses were adjusted to match the optimal hemodynamic functions with nitroprusside and a flexible oral diuretic regimen was designed to maintain fluid balance once optimal hemodynamic functions were achieved. Catheter hemodynamic monitoring was repeated and echo-Doppler and color-flow imaging parameters were reexamined when the patients were receiving a stable dose of an oral vasodilator, before the removal of the pulmonary artery catheter (3 ± 1 days after the initial study). Before discharge, all patients received extensive teaching regarding medications and diet and were given guidelines for adjusting their diuretic doses according to fluctuations in daily home weight measurements. Digoxin was continued throughout the admission and follow-up period in patients receiving it at the time of referral.

Follow-up: After hospital discharge, the patients were followed at the UCLA Cardiomyopathy Center on the tailored therapy designed during acute hemodynamic monitoring. The flexible diuretic regimen was continued, with frequent reinforcement of the initial patient education. Complete echocardiography was once again performed 6 ± 2 months after the baseline study. Estimates of severity of symptoms and physical examination (using the aforementioned scales) were also repeated at that time, before knowledge of echocardiographic findings. All 14 patients were outpatients at the time of follow-up.

Inter- and intraobserver variability and statistical analysis: Interobserver variability, determined from repeat tracings of 40 randomly selected measurements by a second blinded observer, was small for both atrial volumes ($Y = 1.2X - 8 \pm 11$ cm^3, $r = 0.91$) and regurgitant color-flow fractions ($Y = 0.93X + 0.05 \pm 0.06$, $r = 0.84$). Intraobserver variability (duplicate measurements of 60 randomly selected tracings by the initial observer) was also minimal for regurgitant area ($Y = 0.97X + 0.27 \pm 2.1$ cm^2, $r = 0.94$) and atrial volume ($Y = 1.0X + 0.5 \pm 18$ cm^3, $r = 0.86$) measurements. Because these findings for our laboratory are consistent with previously reported data,[5,7] a 10% change was considered significant for valvular regurgitation and atrial volume data. Analysis of variance for repeated measures and paired Student's *t* tests were used to assess acute and long-term changes in echocardiographic and hemodynamic variables.

RESULTS

Changes in medical regimens: At the time of presentation, 12 of the 14 patients were receiving vasodilators; 8 were receiving captopril (mean daily dose 66 ± 78 mg), 3 hydralazine (113 ± 78 mg) and 1 enalapril (5.0 mg). After the acute therapy, all discharged patients were receiving vasodilators, with 10 patients receiving captopril (mean daily dose 300 ± 128 mg), 3 patients receiving hydralazine (533 ± 92 mg) and 1 patient receiving enalapril (5.0 mg). At 6-month follow-up, the vasodilator doses were similar to those at discharge (7 patients receiving captopril—240 ± 127 mg, 4 receiving hydralazine—500 ± 100 mg, 3 receiving enalapril—7 ± 2 mg). Isosorbide dinitrate was part of the medical regimen for 3 patients at the time of referral (mean daily dose 98 ± 61 mg), for 12 at discharge (135 ± 62 mg), and for 13 at follow-up (123 ± 67 mg). All but 1 patient were receiving a diuretic drug at presentation (124 ± 66 mg/day of furosemide), and all 14 patients were doing so at discharge (138 ± 56 mg) and follow-up (153 ± 62 mg). Eleven patients were receiving digoxin on admission; this was continued throughout the study.

Effect of acute therapy on hemodynamic functions: After 3 ± 1 days of hemodynamically guided vasodilator and diuretic therapy, the study patients had significant reductions in mean pulmonary artery wedge and right atrial pressures in addition to a marked increase in forward stroke volume (Table I), similar to that previously reported.[3] There were also significant decreases in mean pulmonary artery pressure (from 44 ± 6 to 30 ± 5 mm Hg), systemic vascular resistance (from 1,760 ± 460 to 1,010 ± 310 dynes·s·cm^{-5}) and pulmonary vascular resistance (from 340 ± 130 to 200 ± 60 dynes·s·cm^{-5}). Mean systolic blood pressure decreased only 10% (from 104 ± 11 to 94 ± 8 mm Hg) and mean heart rate was unchanged after acute therapy (from 93 ± 18 to 95 ± 14 beats/min). Serum creatinine did not change significantly (from 1.1 ± 0.3 to 1.3 ± 0.3 mg/dl). At least 1 liter of fluid was removed from each patient, with a mean diuresis of 4.4 ± 3.6 liters.

Early and sustained reduction of valvular regurgitation: Mitral regurgitation was initially present in all 14 study patients and declined significantly by all 3 measurement techniques during the study ($p < 0.01$ by analysis of variance). Individual values for the color-flow fraction before and after acute therapy and at 6-month follow-up are listed in Table I. After acute therapy, mitral regurgitation also decreased significantly when determined by visual estimate (from 2.0 ± 1.0 to 1.1 ± 1.0) and velocity volume index (from 34 ± 21 to 17 ± 19) (both $p < 0.001$). In each patient, there was a decrease of ≥15% in mitral regurgitation by velocity-volume index after acute therapy. Tricuspid regurgitation was initially detected in 13 of 14 patients and also was significantly reduced by a mean of 41% with therapy as measured by color-flow fraction ($p < 0.01$, Table I). Tricuspid regurgitation decreased acutely by visual estimate, from 1.8 ± 0.7 to 1.1 ± 0.9, and by velocity volume index from 27 ± 14 to 8 ± 10 (both $p < 0.01$). There was an acute reduction of ≥15% by velocity-volume index in all patients. At 6 ± 2 months, the initial improvements in mitral and tricuspid regurgitation were sustained. Mean visual estimates of mitral and tricuspid regurgitation were then 1.3 ± 1.1 and 0.6 ± 0.8, respectively, and velocity volume indexes were 15 ± 14 and 5 ± 6, respectively. These values are significantly reduced from baseline values ($p < 0.01$), and there was a trend of a further reduction in tricuspid regurgitation at 6-month follow-up, but there was no significant change from the second echocardiogram (after acute therapy) in either tricuspid or mitral regurgitation.

Early and late reduction of atrial volumes: Acceptable tracings for the calculation of right and left atrial volumes were obtained for all 3 time points in 12 of 14 and 13 of 14 patients, respectively. Mean right and left atrial volumes were both initially greater than twice normal (normal = 39 ± 12 ml and 38 ± 10 ml, respectively[7]) and decreased significantly ($p < 0.01$ by analysis of variance) (Figure 1). There was a reduction of ≥10% in right and left atrial volumes after the initial therapy in 92% of patients, with a decrease in mean right atrial volume from 85 ± 23 to 64 ± 23 cm^3 and in mean left atrial volume from 100 ± 25 to 80 ± 19 cm^3 ($p < 0.01$ for both). There were further reductions in both mean

TABLE I Effect of Therapy on Hemodynamics and Valvular Regurgitation

	Cardiac Output (liters/min)		PAW (mm Hg)		RA (mm Hg)		Mitral Regurgitation (CFF)			Tricuspid Regurgitation (CFF)		
Pt.	Baseline	Acute Therapy	Baseline	Acute Therapy	Baseline	Acute Therapy	Baseline	Acute Therapy	Six-Month Follow-Up	Baseline	Acute Therapy	Six-Month Follow-Up
1	4.0	8.6	38	20	10	8	0.58	0.20	0.17	0.31	0.11	0.10
2	3.5	5.4	20	15	10	4	0.29	0.23	0	0.32	0.16	0.11
3	3.0	7.4	32	16	15	9	0.51	0.25	0.33	0.40	0	0
4	2.7	4.9	22	20	3	6	0.29	0.26	0.25	0.51	0.28	0.25
5	2.2	3.4	28	16	14	5	0.56	0.24	0.50	0.53	0.17	0.36
6	3.9	4.1	28	9	6	1	0.36	0	0.05	0	0	0
7	2.5	4.9	38	24	20	12	0.61	0.56	0.38	0.52	0.31	0
8	2.7	3.3	32	24	14	6	0.49	0.46	0.45	0.44	0.31	0
9	2.4	5.6	36	12	15	6	0.23	0.15	0	0.13	0.18	0
10	3.5	6.0	23	15	16	10	—	—	—	—	—	—
11	5.5	5.4	36	14	8	6	0.25	0	0	0.12	0	0
12	4.5	7.4	30	14	13	4	0.09	0	0	0.29	0	0.15
13	3.9	4.8	29	20	18	10	0.24	0	0.26	0.46	0.14	0.15
14	3.4	4.4	30	22	22	16	0.20	0	0	0.25	0	0
Mean ± SD	3.4 ± 0.9	5.4 ± 1.5*	30 ± 6	17 ± 4*	13 ± 5	7 ± 4*	0.33 ± 0.16	0.13 ± 0.12*	0.09 ± 0.11*	0.36 ± 0.16	0.18 ± 0.18	0.18 ± 0.18*

* $p < 0.001$ compared to baseline. CFF = color flow fraction; PAW = pulmonary artery wedge pressure; RA = right atrial pressure; SD = standard deviation; — = data not available.

TABLE II Effect of Therapy on Symptoms and Signs of Congestive Heart Failure

	Baseline	Six-Month Follow-Up
Orthopnea	2.9 ± 1.2	0.2 ± 0.3*
Gastrointestinal symptoms	1.3 ± 1.4	0.1 ± 0.3*
JVD	2.5 ± 1.4	0.5 ± 0.8*
Rales	0.5 ± 0.9	0.0 ± 0.0
Ascites	0.7 ± 0.8	0.1 ± 0.5*
Edema	1.1 ± 1.1	0.1 ± 0.3*

* p<0.05

All parameters based on 0 to 4 scale of increasing severity (see text).

Values are mean ± standard deviation.

JVD = jugular venous distention.

right (to 52 ± 14 cm^3) and left atrial volumes (to 65 ± 15 cm^3) at 6 months (p = 0.01 for both), with a further reduction of ≥10% in 64 and 69% of patients, respectively.

Reduction of pulmonary hypertension: The acceleration time of the right ventricular outflow increased with acute therapy in 83% of patients, from a mean of 73 ± 13 to 102 ± 16 ms (p <0.01); this change was sustained at 6-month follow-up (103 ± 27 ms). There was a significant correlation between mean pulmonary artery pressures estimated by the acceleration time and the values obtained from the pulmonary artery catheter before and after acute therapy (r = 0.67, p <0.001). The group mean of the estimated mean pulmonary artery pressure decreased from 42 ± 5 to 30 ± 7 mm Hg acutely (p <0.001), then remained unchanged at follow-up (30 ± 11 mm Hg).

Long-term changes in symptoms and signs of congestive heart failure: At 6 months, congestive symptoms were improved in all patients compared with baseline symptoms (Table II) (p <0.01). Orthopnea, the most prominent symptom in this group, was initially present in 13 of 14 patients, but was absent in all but 2 patients at follow-up. Elevated jugular venous pressure, ascites and edema were also significantly reduced (p <0.01). Rales, which have been shown to be an insensitive marker of high pulmonary artery wedge pressures in chronic heart failure,[10] were present in 4 patients at presentation and in no patients at late follow-up.

Similarity between study patients and those without long-term follow-up: The patients who underwent acute therapy but not long-term follow-up echocardiography were not different from those in the study group in initial hemodynamic variables, ejection fraction (17 ± 4 vs 16 ± 3%) or other echocardiographic parameters, except for a greater amount of tricuspid regurgitation by velocity-volume index (43 ± 24 vs 26 ± 14) (p <0.01). The patients without long-term follow-up also had similar responses to acute therapy in regard to both invasive hemodynamic measurements and echocardiographic parameters (compared with the study group, difference not significant for all).

DISCUSSION

This study demonstrates that early decreases in atrial volumes and in atrioventricular valve regurgitation caused by hemodynamically guided afterload reduction therapy can be maintained with oral agents in survivors with advanced heart failure. This improvement was accompanied by a reduction of congestive symptoms. Although acute afterload reduction has been shown to decrease mitral regurgitation in patients with congestive heart failure,[11] it had not previously been determined whether these initial physiologic improvements could be sustained on long-term oral therapy.

Sustained improvement with therapy initially tailored to hemodynamic goals: Long-term maintenance of the acute reductions in valvular regurgitation and pulmonary hypertension and further decreases in atrial volumes were achieved by continuing the oral vasodilator regimen tailored to the initial hemodynamic response. The short-term hemodynamic responses to captopril and hydralazine in patients with congestive heart failure have not previously been considered predictive of subsequent clinical response.[12,13] However, the therapy used in this protocol was directed at specific hemodynamic goals chosen to decrease both filling pressures

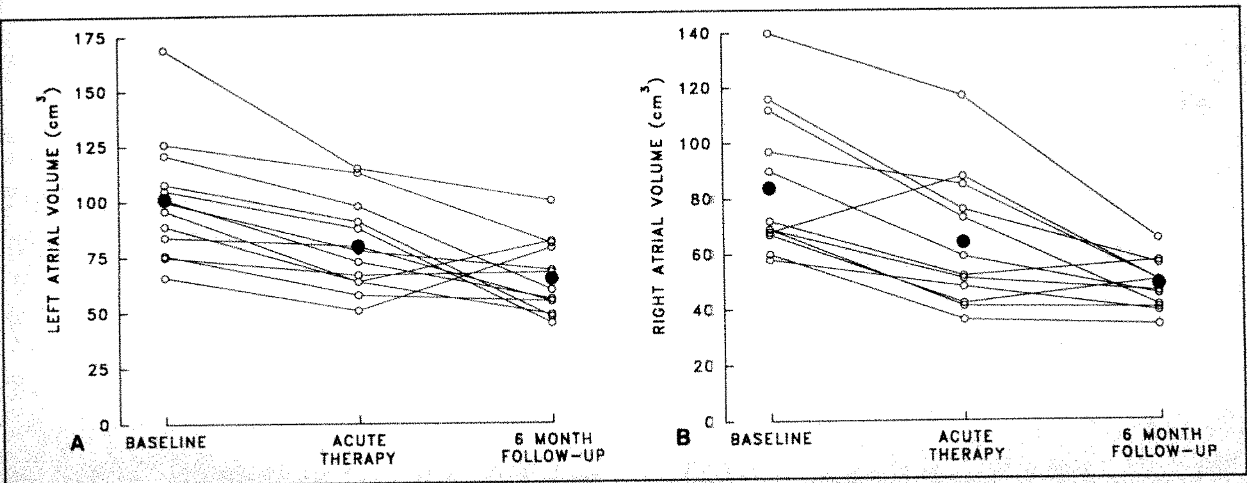

FIGURE 1. ***A,* left and *B,* right atrial volumes were reduced with acute, tailored afterload reduction therapy (p <0.01) and decreased further with chronic oral therapy (p <0.01). Mean values are represented by a *solid circle.***

and systemic vascular resistance. Achievement of these goals required higher vasodilator doses than those used during hemodynamic monitoring in the previous studies. Simultaneous diuresis was also necessary, subsequently maintained by a patient-adjusted flexible diuretic regimen. Diuretic doses have often been fixed or even decreased during titration of vasodilators in some previous studies.[14]

Importance of sustained reductions in valvular regurgitation and atrial volumes: Functional valvular regurgitation, which is routinely present in patients with advanced heart failure,[15] increases congestive symptoms and signs in both the pulmonary venous and systemic venous systems (orthopnea, anorexia, ascites and edema). The long-term clinical improvement seen in the survivors in this study derives at least in part from sustained reduction of these parameters of atrial overload. Reduction of regurgitation is also the major determinant of increased forward cardiac output from afterload reduction therapy[11]; thus, the persistent reduction in valvular regurgitation seen in this study would be expected to contribute to the maintenance of improved systemic perfusion.

The initial and continued decrease in atrial volumes may be a passive reflection of the reductions in mitral and tricuspid regurgitation and volume status. However, atrial geometry itself is one of the determinants of the regurgitant orifice size of the atrioventricular valves of patients without structural valvular disease.[16] Therefore, the decrease in atrial volumes may actually contribute to the reduction of regurgitation and therefore the improvement in forward output seen with vasodilator therapy. It is possible that the reduction in right atrial volume also contributed to clinical improvement by restoring atrial natriuretic factor release responsiveness[17] or by improving the reflex sensitivity between the right side of the heart and the kidneys in response to acute volume changes.[18]

Study limitations: Follow-up echocardiography was performed only in patients with advanced heart failure who survived ≥3 months and had not undergone cardiac transplantation, so these data cannot be extrapolated to all patients with heart failure. However, because the initial ejection fraction and hemodynamic data, as well as the response to acute therapy of those who had follow-up studies, were similar to those who did not, and because all the outpatient deaths were sudden and all but one of the transplants were performed on people waiting as outpatients, there was no selection bias for patients initially less hemodynamically compromised. However, we must emphasize that these data reflect the results of therapy in survivors, and it is possible that some of the patients who died early after the initiation of therapy did have some hemodynamic deterioration.

Right-sided cardiac catheterization was not repeated at follow-up, but the reliability of echocardiography in detecting hemodynamic changes in these patients has already been established.[3] Because all patients had substantial initial improvement in response to therapy, we could not determine correlations between hemodynamic and echocardiographic changes or identify whether the long-term outcome would have been different in patients without an early response. It was also not possible in this population of severely ill patients to perform a "controlled" trial, without providing acute therapy to one group.

Role of echocardiography: Physical examination is often insensitive to hemodynamic status in patients with advanced heart failure,[10] but invasive hemodynamic assessment involves significant expense and discomfort. This study demonstrates the potential value of echocardiography as a noninvasive cardiac imaging and hemodynamic tool for serial outpatient monitoring of the hemodynamic status in this patient population. It gives important information regarding response to therapy and clinical stability by providing parameters of atrial overload as well as an estimate of the severity of pulmonary hypertension.

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Frequency and Severity of Mitral Regurgitation One Year After Balloon Mitral Valvuloplasty

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Mitral regurgitation (MR) was evaluated by Doppler echocardiography in 59 patients with mitral stenosis before, immediately after and 1 year after balloon mitral valvuloplasty (BMV). The severity of MR was graded on a scale from 1+ to 4+. Echocardiographic and hemodynamic variables were analyzed to study the potential factor(s) that might predict the long-term persistence of MR. Echocardiographic variables were mitral valve thickness and motion, subvalvular change, left atrial dimension, commissural calcification and effective balloon/mitral anular diameters. Hemodynamic variables were mitral pressure gradient, pulmonary arterial pressure, ejection fraction, mitral valve area index, age, gender and cardiac rhythm. Mitral valve area index increased from 0.9 ± 0.5 to 1.5 ± 0.8 cm^2/m^2 immediately after BMV, and to 1.4 ± 0.3 cm^2/m^2 at 1-year follow-up ($p < 0.01$). Immediately after BMV, MR grading did not change in 30 patients (51%), increased by 1+ in 23 patients (39%), by 2+ in 2 patients (3.3%) and by 3+ in 2 patients (3.3%), and decreased by 1+ in 2 others. At 1-year follow-up, only 1 patient with severe MR required valve replacement. Fifty-one patients (88%) had no change in the extent of MR ($\leq$1+) and 6 patients (10%) had a 1-grade decrease in their MR; only 1 patient had a 1-grade increase in MR. No clinical or hemodynamic variables or morphologic characteristics of the mitral valve could predict the development of significant MR after BMV. It is concluded that an increment in MR severity $\leq$2+ is frequently seen after BMV. Only a small number of patients (6.7%) developed severe MR ($\geq$3+), and, in some, MR severity might decrease 1 year later.

(Am J Cardiol 1991;67:264–268)

Since the first clinical application of catheter balloon mitral valvuloplasty (BMV) by Inoue et al[1] in 1984, it has become another alternative for the treatment of selected patients with rheumatic mitral stenosis. BMV is more advantageous than surgical commissurotomy, but mitral regurgitation (MR) is an inevitable complication in some patients when the inflated balloon splits the stenosed mitral valve.[2] A significant increase in MR incidence after BMV, from 8 to 13%, has been reported.[3,4] Pulsed Doppler echocardiography has become a useful noninvasive tool in detecting and evaluating MR and its severity.[5] Previous investigators used this technique to assess changes in the severity of MR before and then 1 to 2 days after BMV.[4,6] However, 1-year follow-up changes in MR after BMV have never been reported. The present study was designed to observe the progression of MR 1 year after BMV in 59 patients, to assess which echocardiographic or hemodynamic factor(s) might impact on predictions of the persistence of MR after BMV.

METHODS

Patients: From October 1987 to July 1989, we studied 59 consecutive patients with moderate-to-severe symptomatic mitral stenosis who underwent BMV. Eight patients were in New York Heart Association functional class I, 44 patients were in class II and 7 patients were in class III. Thirty-six patients had atrial fibrillation and 23 had sinus rhythm. Three patients had had previous surgical mitral commissurotomy. Forty-two patients underwent the single- and 17 the double-balloon technique.

Hemodynamic studies: BMV was performed in all patients via the transeptal approach with either the single- or double-catheter balloon technique (Mansfield). Balloon sizes were selected according to the mitral anular diameter, which was predetermined from the average of the mitral anular diameter obtained from 3 (long-axis parasternal, 4- and 2-chamber apical) views seen on 2-dimensional echocardiograms. The effective balloon diameter in the double-balloon technique was calculated from the method proposed by Radtke et al.[7]

All patients underwent right- and left-sided cardiac catheterization. Hemodynamic variables, including cardiac output and mitral pressure gradient, were measured before, immediately after and 1 year after BMV. Mitral valve area was derived from Gorlin's formula and cardiac output was determined by the Fick method.

Echocardiographic studies: All patients were studied with M-mode, 2-dimensional and pulsed Doppler

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echocardiography within 3 days before, 24 hours after and 1 year after BMV, using either a Hewlett-Packard model 77020A ultrasound system equipped with a 2.5-MHz phased-array transducer, or an Irex Meridian ultrasound system equipped with a 2.25-MHz phased-array transducer. MR was assessed by pulsed Doppler echocardiographic examination in the 4- and 2-chamber apical views (Figure 1). Grading was assessed by the extent of the regurgitant jet within the left atrium during systole.[5] The Doppler sample volume was swept thoroughly at various levels of the left atrium, with particular care in determining the maximal flow of the regurgitant jet.

The morphologic features of mitral valve and subvalvular apparatus, including commissural calcification, mitral valve motion, mitral valve thickness and subvalvular change, were graded and scored according to our previous work.[8] Measurements of mitral valve motion and thickness are shown in Figure 2.

Data analysis: All echocardiographic images were recorded on both strip chart paper and videotape for playback analysis. Echocardiographic measurements were performed by 2 investigators without previous knowledge of catheterization data, and the final report reflected their consensus. The left atrial dimension was measured according to the recommendations of the American Society of Echocardiography.[9] We used the mean value of 5 measurements in patients with sinus rhythm and of 10 measurements in patients with atrial fibrillation. Mitral valve area/body surface area was defined as the mitral valve area index. The method used to assess the severity of MR was similar to that previously used by Abbassi et al[5] (Figure 1).

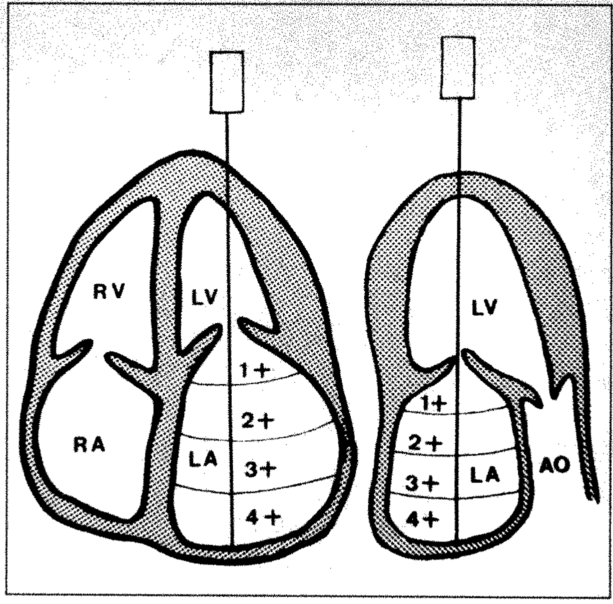

FIGURE 1. Mitral regurgitation assessed by pulsed Doppler echocardiographic examination in apical 4-chamber *(left)* and 2-chamber *(right)* views, grading from 1+ to 4+, according to the extent of the regurgitant jet within the left atrium during systole. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Statistical analysis: The Mann-Whitney rank sum test was used in all patients to compare the difference among preoperative factors with or without enhanced MR: (1) clinical and hemodynamic aspects—age, gender, mitral valve area index, mitral pressure gradient, left atrial dimension, pulmonary arterial pressure and ejection fraction; and (2) morphologic features—commissural calcification, subvalvular changes, mitral valve motion and thickness. The Friedman's analysis of variance test was used for analysis of serial changes in mitral valve area index, mitral pressure gradient and cardiac index. In addition to all these factors, cardiac rhythm, the number of balloon catheters used, effective balloon diameter/body surface area and effective balloon diameter/mitral anular diameter were examined by multiple stepwise logistic regression analysis to identify potential predictors that could induce or enhance the severity of MR immediately and 1 year after BMV.

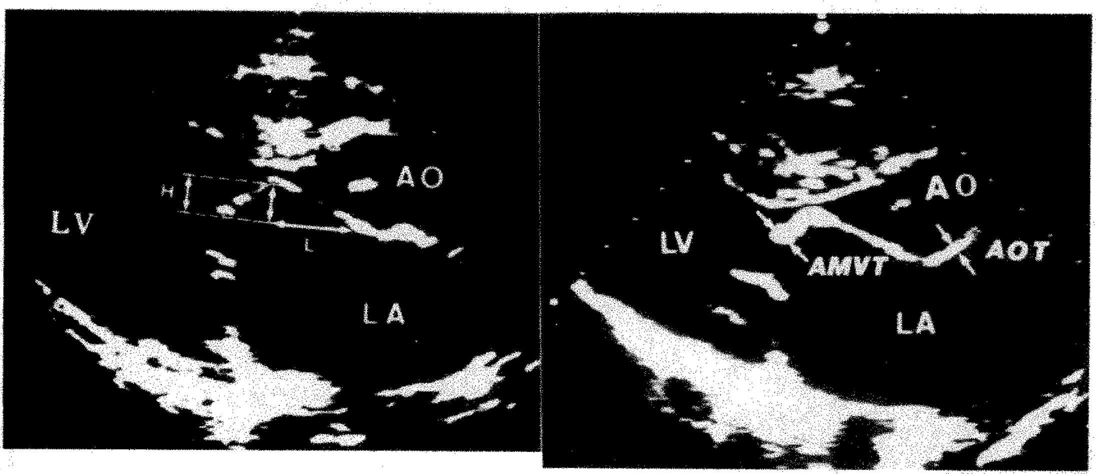

FIGURE 2. At early diastole and in long-axis parasternal view. *Left panel,* measurement of mitral valve motion. Draw a horizontal line from the edge of anterior mitral leaflet to the margin of posterior aortic root where the aortic valve rises. Then draw a vertical line from the center of the dome of the anterior mitral leaflet to the horizontal line. The length from the crosspoint to the dome and the posterior aortic root are referred to as H and L, respectively. The ratio of H/L is the slope of anterior mitral valve motion. *Right panel,* measurement of mitral valve thickness. The ratio of AMVT/AOT is mitral valve thickness. AMVT = thickness of anterior mitral leaflet; AOT = thickness of posterior wall of aortic root; other abbreviations as in Figure 1.

All results are expressed as mean ± standard deviation. A value <0.05 was considered statistically significant.

RESULTS

Clinical hemodynamic and echocardiographic variables: After BMV, all patients had significant improvement in their functional class. Mitral valve area index increased from 0.9 ± 0.5 to 1.5 ± 0.8 cm^2/m^2 ($p < 0.01$) immediately after BMV, and to 1.4 ± 0.3 cm^2/m^2 at 1-year follow-up. Cardiac index increased from 2.7 ± 1.0 to 3.5 ± 1.2 liters/min/m^2 ($p < 0.01$) after the procedure, and to 3.1 ± 1.3 liters/min/m^2 1 year later. Mitral pressure gradient decreased from 18 ± 7 to 10 ± 5 ($p < 0.05$) and to 11 ± 6 mm Hg, respectively (Figure 3).

Echocardiographic grade and score for preoperative morphologic characteristics of mitral valve subvalvular apparatus are listed in Table I. By univariate analysis, patients with an increase in MR had larger scores in subvalvular change than those without (1.4 ± 0.7 vs 0.9 ± 0.8, $p < 0.05$). Nevertheless, multiple stepwise logistic regression analysis revealed that no factors, including morphologic characteristics and preoperative clinical and hemodynamic variables, would predict the enhancement and persistence of MR both immediately and 1 year after BMV.

Mitral regurgitation: Before BMV, 45 patients (76%) had no MR; 13 patients (22%) had 1+ MR and 1 patient (1.7%) had 2+ MR. Immediately after BMV, 24 patients (41%) had no MR and 6 patients (10%) remained at 1+. Of the remaining patients, 27 (46%) had a different extent of increase in MR after BMV. The increase in MR severity was noted to be 1+ in 23 patients (39%), 2+ in 2 patients (3.3%) and 3+ in 2 patients (3.3%). One patient, who had an increase in MR from 1+ to 4+ after BMV, received a mitral valve replacement 9 months later. Compared with the results immediately after BMV, 25 patients (43%) had no detectable MR at 1-year follow-up, 26 patients (45%) had 1+ MR and 6 patients (10%) had a 1-grade decrease in MR, with the MR grade in 3 patients decreasing from 3+ to 2+, and decreasing from 2+ to 1+ in the other 3. Only 1 patient had a further 1-grade increase in MR (Figure 4).

DISCUSSION

Doppler echocardiography was found to be highly sensitive and specific for the detection of MR.[10] According to previous reports,[11-14] about 9 to 20% of patients who underwent surgical mitral commissurotomy developed MR, and 8 to 20% of them had significant worsening of MR after the operation. Poor prognosis has been documented in these patients.[15]

Because BMV splits the fused commissures of the mitral valve, MR is a potential complication of BMV. In the present study, 46% of patients had newly devel-

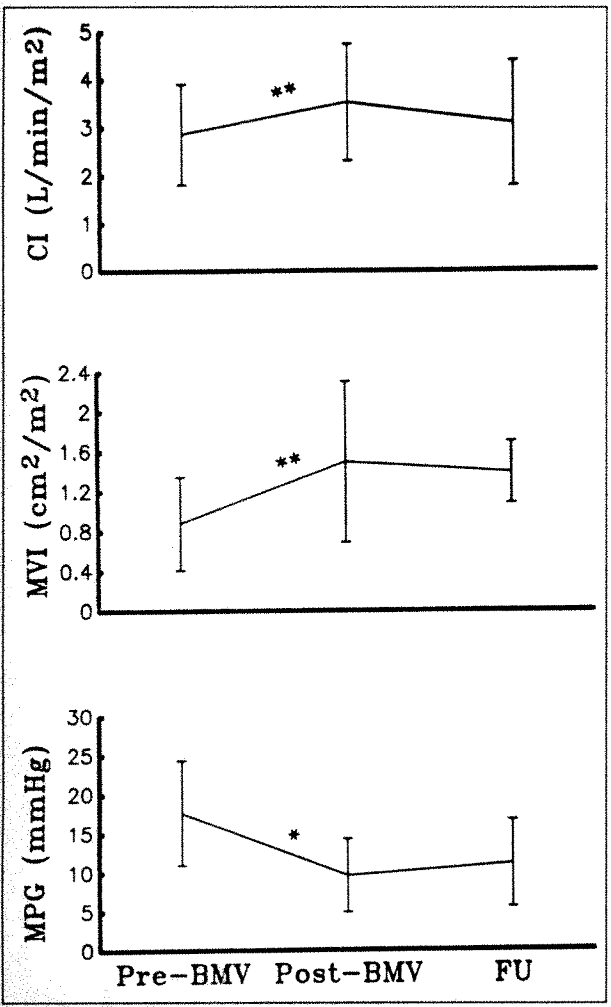

FIGURE 3. Serial changes in mitral valve area index (MVI), cardiac index (CI) and mitral pressure gradient (MPG) before balloon mitral valvuloplasty (pre-BMV), immediately after (post-BMV) and at 1-year follow-up (FU). *p <0.05; **p <0.01.

TABLE I Variables in Patients With or Without Increase in Mitral Regurgitation After Balloon Valvuloplasty

Variables	Without MR Increase (n = 31)	With MR Increase (n = 28)	p Value
	Clinical and Hemodynamic		
Age (yr)	43 ± 11	42 ± 16	NS
EBD/BSA	18 ± 2	18 ± 2	NS
EBD/MAD	0.9 ± 0.1	0.9 ± 0.1	NS
EF (%)	45 ± 9	42 ± 12	NS
LAD (cm)	5.1 ± 0.7	5.1 ± 0.8	NS
MPG (mm Hg)	12 ± 7	12 ± 11	NS
PAP (mm Hg)	54 ± 23	53 ± 23	NS
MVI (cm^2/m^2)	0.9 ± 0.3	0.8 ± 0.2	NS
	Morphologic		
CC grade	1.4 ± 0.8	1.6 ± 0.6	NS
MVM grade	0.4 ± 0.1	0.4 ± 0.1	NS
MVM score	0.8 ± 0.7	0.8 ± 0.7	NS
MVT grade	1.8 ± 0.8	1.7 ± 0.9	NS
MVT score	0.8 ± 0.7	0.8 ± 0.7	NS
SVC grade	0.9 ± 0.8	1.4 ± 0.7	<0.05

CC = commissural calcification; EBD/BSA = effective balloon diameter/body surface area; EBD/MAD = effective balloon diameter/mitral anular diameter; EF = ejection fraction; LAD = left atrial dimension; MPG = mitral pressure gradient; MVI = mitral valve area index; MVM = mitral valve motion; MVT = mitral valve thickness; NS = not significant; PAP = pulmonary artery pressure; SVC = subvalvular change.

oped or increased MR immediately after BMV, in accordance with previous reports (32 to 46%).[4,6,16] This study shows that MR is not a major problem after BMV. Our results reveal that, immediately after BMV, only 4 of 59 patients (7%) had an increase in MR of >2+. Patients with severe MR (≥3+) presented with splitting or commissures instead of with fracture of valve leaflets or tearing of chordae tendineae. Only 1 patient (1.7%) required valve replacement because of a fracture of the ring anulus by an oversized balloon. Surprisingly, there were 2 patients—1 with 2+ and another with 1+ MR before BMV—who achieved a 1-grade reduction of MR. The reason for the decrease in MR severity after BMV might be a relatively better coaptation of the unsmooth margin of the diseased valve leaflet, separated by the catheter balloon.

At 1-year follow-up, 6 patients (22%) with worsened MR immediately after BMV had a 1-grade decrease in MR. The slight decrease in mitral valve area and the increase in pressure gradient (Figure 3) from immediately to 1 year after BMV suggests that there was a refusion of the split commissures of the mitral valve, which might contribute to the decrease in the extent of MR.

Unlike previous grading and scoring systems,[4,17] different criteria were used to evaluate the morphologic characteristics of the mitral valve in this study. First, we measured the ratio of thickness between the anterior mitral leaflet and the posterior wall of the aortic root to assess the mitral valve thickness as a factor to negate the effect of gain control. Second, we measured the slope of the diastolic doming of the anterior mitral leaflet to reflect the severity of commissural adhesion and the pliability of mitral valve motion. The echocardiographic score of valvular or subvalvular morphologic abnormalities did not distinguish between patients with or without an increase in MR immediately after BMV.[4] Chen et al[6] reported that 2 variables could predict an increase in MR: (1) the ratio of the sum of 2 balloons and the mitral anulus diameter, and (2) the severity of subvalvular change. However, multiple stepwise logistic regression analysis in this study revealed that an increase in MR could not be predicted from any clinical or hemodynamic variables and morphologic characteristics of the mitral valve.

The grading of the severity of MR by pulsed Doppler echocardiography correlated well with the findings of left ventriculography in our laboratory in a series of 108 patients[18] (κ value = 0.77), which was as good as the report of Pons-Llado et al.[19] The interobserver reproducibility in the quantitation of the extent of MR has been quite good (κ value = 0.85) in our previous work.[18]

In conclusion, MR is a complication frequently seen after BMV. Only a small number of patients (6.7%) had severe MR (≥3+) in our study. No clinical or morphologic variables can predict the development of significant MR after BMV in these patients. Moreover, at 1-year follow-up, some patients may even have decreased severity of MR by Doppler echocardiography. Therefore, it is suggested that MR is not a major problem in patients undergoing BMV. However, because our patients comprised a small population, further large-scale observations and long-term follow-up in patients who do have MR after BMV may be warranted.

Study limitations: During pulsed Doppler examination, the sampling sites were carefully and progressively moved through various levels in the left atrium. Nevertheless, estimation of the severity of regurgitation by pulsed Doppler echocardiography is a semiquantitative method[20]; the accuracy of regurgitant jet mapping will be affected by several factors: (1) left atrial size and compliance, (2) left ventricular pressure and contractility, (3) the direction of the jet flow, and (4) the character of different machine and transducer settings. Overestimation of MR may occur in patients with a normal or hyperdynamic heart, and normal size of the left atrium with central jet flow. Underestimation may occur in patients with either 1 of left ventricular dysfunction, dilated left atrium, eccentric jet or with a combination of

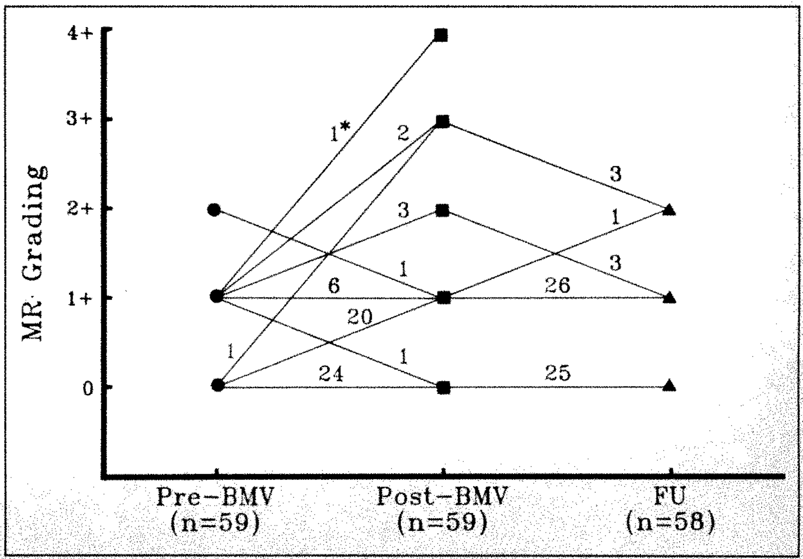

FIGURE 4. Serial changes in mitral regurgitation (MR) of individual patients before balloon mitral valvuloplasty (pre-BMV), immediately after (post-BMV) and at 1-year follow-up (FU). Grading ranged from 0 to 4+. Numbers above lines are numbers of patients. *Patient received prosthetic valve replacement 9 months after BMV.

these factors. We found that either overestimation or underestimation in mapping the severity of MR is frequently seen in cases with grading <2+ and eccentric jet.[18] The application of color Doppler echocardiography may assist to some extent in clarifying these limitations.[21]

Acknowledgment: We thank P.C. Lee for statistical analysis and Y.C. Chan for manuscript preparation.

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Reference Values and Reproducibility of Doppler Echocardiography in the Assessment of the Tricuspid Valve and Right Ventricular Diastolic Function in Normal Subjects

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The Doppler echocardiographic indexes of the tricuspid and mitral valves were assessed in 74 normal subjects (35 women and 39 men, mean age 45 years). A reproducibility study was also performed to examine the various sources of technical and biological variability.

There were significantly higher peak early and late flow velocities across the mitral valve than across the tricuspid valve (0.67 ± 0.13 and 0.47 ± 0.12 vs 0.51 ± 0.08 and 0.35 ± 0.09 $m \cdot s^{-1}$, respectively; all $p < 0.0001$). There was no significant difference between the early:late (E:A) velocity ratios of the 2 valves (1.65 ± 0.73 vs 1.75 ± 0.67, $p < 0.01$). There was a steeper mitral early deceleration slope (-3.59 ± 1.07 vs -2.95 ± 0.91 $m \cdot s^{-2}$) but no significant difference in pressure half-times across the 2 valves (47 ± 7 vs 51 ± 12 ms, $p < 0.1$). No influence of gender or body surface area could be demonstrated. There was a weak but significant relation between mitral peak early, peak atrial velocity and E:A ratio and age ($r = -0.39$, $p < 0.001$, $r = 0.23$, $p < 0.01$, and $r = -0.245$, $p < 0.01$, respectively). There was no significant correlation between any of the tricuspid flow parameters and age. Respiration caused pronounced variability in the tricuspid Doppler indexes and all tricuspid flows were sampled and analyzed only during inspiration. The intra- and interobserver variabilities were small for all of the Doppler indexes measured, but the day-to-day variability was quite significant especially for the pressure half-time, deceleration and acceleration slope values. The present study documents in detail the normal Doppler flow characteristics of the tricuspid valve and compares them with the normal mitral flow parameters in the same subject.

(Am J Cardiol 1991;67:269–273)

In clinical cardiology there has been renewed interest in the assessment of diastolic myocardial function,[1] and the use of transmitral Doppler recordings in assessing left ventricular diastolic performance has received increased attention.[2–5] Transtricuspid pulsed Doppler has been used less often to evaluate right ventricular filling and diastolic dysfunction in ischemic heart disease and restrictive cardiomyopathy,[4,6,7] and it holds promise as a serial noninvasive measure of the response to various therapeutic interventions. The Doppler characteristics of blood flow across the aortic, pulmonary and mitral valves in a normal population with a wide age distribution have been well documented.[8–11] The tricuspid Doppler pressure half-time has been used to assess the severity of tricuspid stenosis in native[12–14] and prosthetic[14,15] valves. However, there is relatively little information about normal tricuspid flows. In the published studies to date dealing with tricuspid Doppler diastolic wave forms, either only the peak velocity is assessed[6–9] or the normal control groups have been relatively small.[4] In addition, before data obtained from the Doppler wave form can be used for longitudinal or cross-sectional studies in patients with cardiac disease, the variability inherent in these Doppler measurements must be understood. Therefore the present investigation was performed to (1) provide a normal adult reference range for Doppler echocardiographic indexes of right ventricular diastolic and tricuspid valve function, and (2) determine the sources of technical and biological variability with this technique.

METHODS

Study group: The study group consisted of 74 normal volunteers (39 men and 35 women, aged 26 to 77 years [mean 45]). All subjects had a normal cardiorespiratory history, physical examination and echocardiogram. Ten people were excluded during selection because of possible cardiovascular or respiratory disease. Thirty of the volunteers smoked cigarettes but had no symptoms or signs of chronic lung disease. We performed a comparative study of mitral and tricuspid Doppler characteristics in the 74 volunteers and a reproducibility study in 25 of these same volunteers.

COMPARATIVE VALVE STUDY

Doppler echocardiography: The combined Doppler echocardiography examination was performed with an

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Advanced Technology Laboratories Ultramark 8 System using a 2.5-MHz pulsed Doppler imaging transducer, with a sample window of 3 × 2 mm^2. The subject lies on his or her left side and measurements were made using a parasternal short-axis plane, an apical 4-chamber plane or a modified position midway between the apex and parasternal short-axis planes. The latter position was most often used for assessing tricuspid valve flow because it gave the best flow alignment with the least wall motion interference; this was important because a lower velocity range and filter settings were required for tricuspid flow in order to improve the resolution. The sample window was placed just distal to the tips of the open atrioventricular valves with minor adjustments made until clear visual and auditory Doppler signals were obtained.

Doppler analysis: The Doppler recordings were made at a sweep speed of 100 mm·s^{-1}. The Doppler spectral display was traced using a tracker ball facility and analyzed using on-line computer software. In each subject the cardiac cycles with the most clearly defined flow velocity wave form, the maximum early diastolic velocity and the steepest descent of early flow velocity were chosen for analysis. The average from 6 cardiac cycles for each valve was taken as the final result.

The following measurements were obtained (Figure 1): (1) peak early inflow velocity (E) m·s^{-1}, (2) peak late atrial velocity (A) m·s^{-1}, (3) ratio of early to late peak atrial velocity ratio (E:A), (4) pressure half-time (ms) by the method of Hatle et al,[11] (5) early deceleration slope (EF) m·s^{-2}, (6) early acceleration slope (OE) m·s^{-2}, and (7) velocity time integral (cm).

Since the flow velocity wave form is displayed as a gray scale line of certain thickness, the points O, E and A on the spectral display were identified as the mid- or modal points of the gray scale spectrum. The slope of the EF or OE lines were similarly defined by drawing a straight line passing through the midportion of the gray scale spectrum. In the instances in which the slope EF was curved rather than a straight line, EF was constructed as the line identifying the maximum measure of the slope. The indexes E, EF slope, pressure half-time and acceleration slope measure events occurring in the early filling phase of diastole, whereas the indexes A and E:A ratio represent a measure of the contribution of atrial systole to ventricular filling.[16]

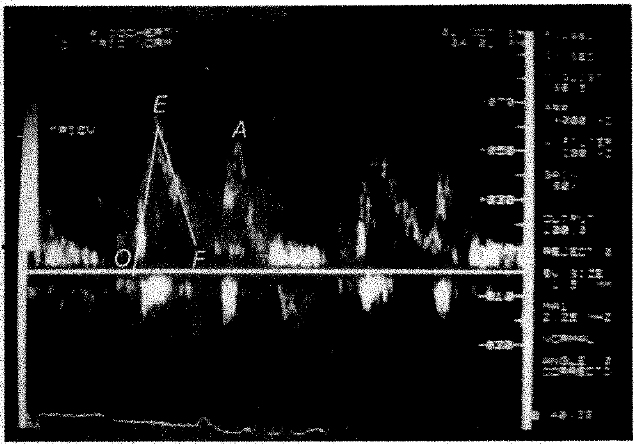

FIGURE 1. Pulsed wave Doppler recording of tricuspid valve flow. A = peak late velocity; E = peak early velocity; F = end of rapid early filling phase; O = onset of early flow.

Preliminary observations: There were marked differences in the effect of respiration on mitral and tricuspid flows. Considerable respiratory variation was seen in the diastolic flow velocity profile for the tricuspid valve with little, if any, variation in mitral valve flow. This marked difference made comparisons between the valves meaningless unless a tricuspid flow pattern from a specific phase of the respiratory cycle was chosen for all measurements. We chose the tricuspid wave form with the maximum early velocity from the inspiratory phase of the respiratory cycle. This gave the clearest spectral display for analysis and the final result was from the average of 6 cardiac cycles. Since there was little important variation in normal mitral flow with respiration, the average from any 6 clear cardiac cycles was taken for comparison.

Statistical analysis: The population was characterized in terms of reference limits: the mean, standard deviation and range were recorded. All significance tests were performed at a $p = 0.05$ level. For each of the variables the hypothesis of no difference between the valves was tested with a Mann Whitney U test or a 2-sample t test depending on the distribution of the results. The relation of the variables with body surface area and age were examined by linear regression analysis and correlation.

REPRODUCIBILITY STUDY

Doppler measurements: The following sources of variability were assessed from the measurements obtained from 25 of the study subjects. All measurements in this part of the study represent the average values from 6 cardiac cycles: (1) intraobserver variability—comparing paired readings obtained by the same observer on 2 separate occasions on the same day; (2) interobserver variability—comparing results obtained and analyzed by 2 observers for the same subject on the same day; (3) day-to-day variability—comparing paired readings obtained by 1 observer from 2 tracings recorded on 2 separate days. This estimate also embodies intraobserver variability; (4) respiratory cycle variation—the maximum difference for each of the variables over a respiratory cycle was determined by 1 observer. The beginning of inspiration and expiration was marked on the recording.

Statistical analysis: The data from the reproducibility study consisted of 25 pairs of measures obtained from 25 subjects for each of the 4 sources of variability assessed in the study. The means of the absolute differences between paired readings were calculated for each source of variability. The mean differences between paired readings were evaluated using the Student's t test. In addition, the upper 95% confidence limit was reported for the distribution of the absolute differences for each Doppler index of diastolic function.

RESULTS

Mitral and tricuspid valve comparative study: The results are listed in Table I. There were significantly higher peak early and late flow velocities across the mitral valve but no significant differences between the E:A ratios for the 2 valves shown. There was a significantly steeper mitral deceleration slope (-3.59 vs -2.95 $m{\cdot}s^{-2}$, $p < 0.001$) but no significant difference in pressure half-times across the 2 values (47 vs 51 ms, difference not significant). The mean acceleration to peak early velocity (8.71 vs 5.81 $m{\cdot}s^{-2}$) and the velocity time integral (11 vs 7 cm) were significantly higher for the mitral valve. No influence of gender or body surface area could be demonstrated. There was a weak but significant relation between the mitral peak early velocity ($r = -0.39$, $p < 0.001$), and mitral peak atrial velocity ($r = 0.23$, $p < 0.01$) and age (Figure 2). The mitral E:A ratio also showed a weak inverse relation with age ($r = -0.245$, $p < 0.01$). There was no significant correlation between any of the tricuspid flow parameters and age. There was no difference in the Doppler parameters of smokers and nonsmokers.

Variability study: The means of the absolute and percentage differences of paired measurements and their upper 95% confidence intervals are listed in Tables II and III, respectively. The intra- and interobserver variability were small for all of the Doppler indexes analyzed. The effect of respiration on tricuspid flow caused significant variation and, as discussed earlier, led to the sampling and analyzing of peak tricuspid flows only during inspiration. The intraobserver and interobserver variabilities were small and not significant. The means of the absolute differences and upper 95% confidence limits for measurements obtained on 2 different days (and analyzed by 1 observer) were larger than those due to observer variability for most of the comparisons. They reached statistical significance only for the acceleration slope measurements, but the confidence limits for the pressure half-time and deceleration slopes

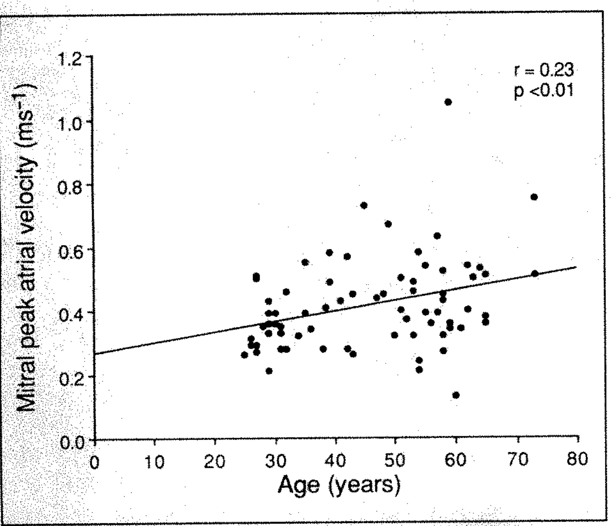

FIGURE 2. Graph showing correlation between age and peak Doppler atrial velocity for the mitral valve.

TABLE I Comparison of Doppler Indexes for Mitral and Tricuspid Valves (n = 74)

	Mitral							Tricuspid						
	E (ms^{-1})	A (ms^{-1})	E/A	Pt1/2 (ms)	Dec. (ms^{-2})	Acc. (ms^{-2})	VTI (cm)	E (ms^{-1})	A (ms^{-1})	E:A	Pt1/2 (ms)	Dec. (ms^{-2})	Acc. (ms^{-2})	VTI (cm)
Mean ± SD	0.67 ± 0.13	0.47 ± 0.12	1.65 ± 0.73	47 ± 9	3.59 ± 1.07	8.71 ± 2.81	11 ± 3	0.51 ± 0.08	0.35 ± 0.09	1.75 ± 0.67	51 ± 12	2.95 ± 0.91	5.81 ± 2.0	7 ± 2
Minimum	0.35	0.14	0.59	30	1.72	4.02	5	0.26	0.07	0.81	26	1.47	2.10	4
Maximum	0.97	0.82	4.5	66	6.92	15.51	19	0.74	0.60	4.0	81	5.85	12.82	15
Differences														
p value	<0.0001	<0.0001	<0.1	>0.5<0.1	0.001	<0.0001	<0.0001							
mitral vs tricuspid														
95% CI	0.09–0.17	0.07–0.15	−0.03–−0.14	0.6–6.7	0.5–1.21	2.2–3.9	2–3.8							

A = peak late atrial diastolic velocity; Acc. = acceleration; CI = confidence interval; Dec. = deceleration; E = peak early diastolic velocity; E:A ratio = peak early to atrial velocity ratio; M = mitral; Pt1/2 = pressure half-time; SD = standard deviation; T = tricuspid; VTI = velocity time integral.

TABLE II Doppler Indexes of Diastolic Function: Means of the Absolute (Percentage) Differences in Measurement Due to Sources of Variability (n = 25)

Variability	E (ms^{-1}) Mitral	E (ms^{-1}) Tricuspid	A (ms^{-1}) Mitral	A (ms^{-1}) Tricuspid	E:A Mitral	E:A Tricuspid	Pt1/2 (ms) Mitral	Pt1/2 (ms) Tricuspid	Deceleration (ms^{-2}) Mitral	Deceleration (ms^{-2}) Tricuspid	Acceleration (ms^{-2}) Mitral	Acceleration (ms^{-2}) Tricuspid
Intraobserver	0.02 (3)	0.01 (2)	0.01 (2)	0.01 (3)	0.15 (9)	0.13 (7)	4 (8)	3 (6)	0.41 (11)	0.35 (11)	0.31 (4)	0.54 (9)
Interobserver	0.03 (4)	0.02 (4)	0.01 (2)	0.02 (6)	0.14 (9)	0.12 (7)	5 (11)	4 (8)	0.33 (9)	0.42 (14)	0.74 (8)	0.82 (14)
Day-to-day	0.06 (9)	0.05 (11)	0.04 (8)	0.03 (9)	0.37 (22)	0.26 (15)	8 (17)	9 (18)	0.9 (25)	0.75 (25)	1.95* (22)	1.73* (30)
Respiration	0.01 (1)	0.11* (24)	0.01 (2)	0.07 (20)	0.09 (5)	0.12 (7)	3 (6)	10* (20)	0.25 (7)	1.31* (44)	0.32 (41)	1.40* (24)

* $p<0.01$.
Numbers in parentheses = percentage difference; abbreviations as in Table I.

were wide. Heart rate was similar and not significantly different on the first and second readings.

DISCUSSION

Mitral versus tricuspid valve: Normal tricuspid flow, in contrast to normal mitral flow, showed marked variation in both flow velocity and profile with normal respiration. This pronounced respiratory variability was noted and analyzed during preliminary observations, and made it necessary to assess tricuspid flow from the same part of the respiratory cycle in order to make meaningful comparisons with mitral valve flow. Inspiratory tricuspid flow was chosen because it gave the maximum flow velocity and clearest spectral display for analysis. The maximal early and late tricuspid diastolic velocities and the velocity time integral were always less than the maximal diastolic velocities across the mitral valve; the tricuspid peak velocity was approximately 70% of the mitral peak velocity. This is because the tricuspid valve area is invariably greater than the mitral valve area and since mean flow across both is the same per cardiac cycle, the velocity of blood on the right side of the heart must be lower. Also, because of the heart position in the chest the Doppler beam is closer to parallel alignment for mitral valve inflow than tricuspid flow and hence will tend to give a higher peak velocity for mitral valve flow. The mitral deceleration slope was significantly steeper than the tricuspid slope, but there was no significant difference between the equivalent half-time values. This discrepancy between slope and half-time might be explained by the differences in peak early diastolic velocities between the 2 valves. The pressure half-time is dependent on the peak velocity; as the peak velocity increases, with the deceleration slope remaining constant, the pressure half-time will also increase proportionately. Therefore, if only pressure half-times were measured, the higher peak early mitral velocity could mask the difference in deceleration slopes. Appleton et al,[4] in the only other study to assess normal tricuspid flow, also found a shorter deceleration time for the mitral valve (199 ± 32 ms) than for the tricuspid valve (221 ± 31 ms), but deceleration slopes or pressure half-times were not reported. A steeper early acceleration slope for the mitral valve was also found.

We found a weak correlation between peak mitral early velocity, atrial velocity or E:A ratio and age and no significant correlation in these same parameters for the tricuspid valve. Previous reports have shown a stronger association betweeen age and Doppler indexes of mitral valve flow (e.g., Sartori et al[17] found a strong negative correlation between mitral early velocity and age [$r = -0.905$, $n = 25$]). However, there have been a few conflicting reports. Wilson et al[8] studied a larger study group ($n = 110$) and reported a wider scatter with a relatively weak correlation between age and peak mitral early velocity ($r = -0.39$); we are unable to explain this difference between groups.

Reproducibility study: The reproducibility study, excluding the effects of respiration, produced very similar results for both valves. The variability analysis suggests

TABLE III Doppler Indexes of Diastolic Function: Upper 95% Limits of the Distribution of the Absolute (Percentage) Differences for Each Index (n = 25)

	E (ms^{-1})		A (ms^{-1})		E:A		Pt1/2 (ms)		Deceleration (ms^{-2})		Acceleration (ms^{-2})	
Variability	Mitral	Tricuspid	Mitral	Tricuspid	Mitral	Tricuspid	Mitral	Tricuspid	Mitral	Tricuspid	Mitral	Tricuspid
Intraobserver	0.05 (7)	0.04 (8)	0.02 (4)	0.04 (11)	0.21 (13)	0.24 (14)	8 (17)	7 (14)	0.68 (19)	0.45 (15)	0.42 (5)	0.74 (13)
Interobserver	0.07 (10)	0.06 (12)	0.03 (6)	0.05 (14)	0.27 (16)	0.23 (13)	9 (19)	7 (14)	0.65 (18)	0.52 (18)	1.23 (14)	1.19 (20)
Day-to-day	0.12 (18)	0.10 (19)	0.07 (15)	0.06 (17)	0.42 (25)	0.35 (20)	16 (34)	17 (33)	1.05 (29)	0.92 (30)	2.46 (28)	2.21 (38)
Respiration	0.03 (4)	0.18 (35)	0.02 (4)	0.14 (40)	0.14 (8)	0.32 (18)	7 (15)	21 (41)	0.37 (9)	1.95 (66)	0.54 (9)	2.69 (46)

Numbers in parentheses = percentage difference; abbreviations as in Table I.

that Doppler indexes of early and late peak velocities for both valves are reliably measured between observers and on a day-to-day basis. The pressure half-times, acceleration and deceleration slopes are certainly reproducible between and within observers; however, their day-to-day variability makes them less reliable as sensitive markers of ventricular diastolic function although quite adequate for the assessment of valvular heart disease. The more marked day-to-day variation is not surprising because this method inherently includes intraobserver variability as well as physiologic changes such as alterations in autonomic tone and ventricular loading conditions, which are known to influence these flow velocities. These variability results are very similar to the only previously reported reproducibility study by Spirito et al[9] for Doppler indexes of mitral valve flow.

Doppler methods: The usual pitfalls that are known to occur in the Doppler assessment of the mitral valve can occur in measuring tricuspid flow. It is important to be close to parallel (<20°) with the direction of blood flow to obtain a clear spectral display and a true velocity profile. This was most often obtained for the tricuspid valve using a modified transducer position midway between the apex and parasternal region. This tended to lengthen the right ventricular inflow region, allowing easier alignment with flow, and also reduced wall motion noise which can be a common problem when using the low filter settings and low velocity Doppler range from the apex. The highest velocities across both valves are recorded with the sample window at or between the tips of the valve leaflets as they open during diastole. The position is important because the velocity curve changes in profile with alterations in sample volume position.[18]

Continuous-wave Doppler across the mitral or tricuspid valves will sum all of the velocities along the Doppler beam. The resultant flow velocity curve will be completely different from a pulsed wave recording and should not be used in the assessment of diastolic function. Heart rate may influence the relative heights of the early and late velocities, but in this study the mitral and tricuspid valves were compared almost simultaneously at identical heart rates.

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Left Ventricular Size, Mass and Function in Relation to the Duration and Quantity of Heavy Drinking in Alcoholics

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Left ventricular (LV) hypertrophy and mild dysfunction are frequently observed in alcoholics but little is known about how they relate to the duration and severity of alcohol abuse. LV size, mass and function were studied using echocardiography and systolic time intervals in 78 middle-aged male alcoholics who also gave detailed accounts of the duration of heavy drinking, the quantity of recent ethanol consumption and the duration of abstinence. Compared with 34 healthy nonalcoholics, alcoholics had a higher LV mass index (85 ± 2 [mean ± standard error] vs 77 ± 2 g/m², p = 0.001), a thicker posterior wall (11 ± 0.2 vs 10 ± 0.2 mm, p = 0.02), a longer end-systolic diameter index (18 ± 0.3 vs 17 ± 0.3 mm/m², p = 0.02), and a higher preejection period/ejection time ratio (0.36 ± 0.01 vs 0.33 ± 0.01, p = 0.002). In multivariate linear regression models, these abnormalities proved independent of the drinking history, except that posterior wall thickness was weakly related to the duration of heavy drinking (standardized correlation coefficient 0.36, p = 0.01). Univariate analyses suggested that the LV mass index and systolic time interval ratio had, if anything, a curvilinear relation to the total duration of heavy alcohol consumption. It is concluded that the LV hypertrophy and dysfunction found in alcoholics are poorly related to the duration and severity of self-reported alcohol abuse. Together with other data, this suggests that there is no simple linear dose-injury relation in the long-term cardiotoxicity of ethanol. Factors modifying the myocardial effects of ethanol need to be studied more in the future.

(Am J Cardiol 1991;67:274–279)

Subclinical alcoholic heart muscle disease is characterized by left ventricular (LV) hypertrophy,[1,2] mild systolic[3–6] or diastolic[7,8] dysfunction, or both, an impaired response to afterload challenge or dynamic exercise,[9,10] and a liability to arrhythmias.[11,12] Whether, and to what extent, these abnormalities depend on the duration and quantity of alcohol abuse is still seldom studied and the data are controversial.[2,3,5] We therefore examined a comparatively large number of chronic alcoholics to see if their LV size, mass or function, as determined by echocardiography and systolic time intervals, relate to the details of their drinking histories. The present report contains results of pertinent univariate and multivariate analyses and compares alcoholics with age- and sex-matched nonalcoholics.

METHODS

Alcoholics: A total of 85 alcoholics were consecutively hospitalized for detoxification and research purposes. For inclusion into our study they had to be free of history, signs and symptoms of any cardiovascular, metabolic or respiratory disease. The final study group comprised 78 male alcoholics aged 27 to 56 years (mean 39).

Protocol: The day after admission the patients underwent routine laboratory testing to study, among other parameters, hematology (Coulter autoanalyzer), serum electrolytes (ion-selective electrodes), serum aspartate and alanine aminotransferases (enzymatic) and serum gammaglutamyltransferase (enzymatic). A 12-lead electrocardiogram (50 mm/s) and a chest x-ray were also obtained.

The studies in the cardiovascular laboratory were made after detoxification. In addition to a routine clinical examination, the subjects were carefully questioned regarding the total duration of heavy alcohol consumption (years), the length of the last uninterrupted drinking period (weeks) and the length of abstinence (days). They were also asked to specify the types and amounts of alcoholic drinks typically consumed in 1 day during a drinking bout. These were converted to grams of absolute ethanol and added up to produce an estimate of daily consumption. The quantity of recent ethanol exposure (g/kg) was calculated by multiplying the estimate of daily consumption by the number of days in the last drinking period and dividing the product by body weight. Current quantitative smoking habits (number of cigarettes consumed daily) were also recorded.

After the clinical assessment and interview, the subjects underwent an echocardiographic LV examination

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and determination of the systolic time intervals. Blood pressure was measured by the cuff method. The study protocol was approved by the institutional ethics committee, and each subject gave verbal informed consent.

Echocardiography: Ultrasound studies were made using a cross-sectional scanner (Irex System III or Toshiba SSH-60A) equipped with 2.25- and 3.75-MHz phased-array transducers and a strip-chart recorder. M-mode echoes of the left ventricle were recorded together with an electrocardiogram and an external phonocardiogram, using a technique that has been described in detail elsewhere.[13] The chart speed was 100 mm/s. Analyzable studies were obtained in 68 alcoholics (87%). The following LV measurements were determined and averaged over 5 consecutive, technically acceptable cardiac cycles, as previously detailed[13,14]: end-diastolic diameter, end-systolic diameter, posterior wall thickness, mass, fractional shortening and peak diameter lengthening rate. The cavity diameters and mass were divided by body area to get the respective normalized indexes. Heart rate was derived from the RR intervals in the electrocardiogram.

Systolic time intervals: An indirect carotid artery tracing, a high-frequency external phonocardiogram and an electrocardiographic lead accurately displaying the onset of depolarization were recorded simultaneously at the speed of 100 mm/s. High-quality tracings were obtained in 66 subjects (85%). The preejection period and its ratio to the LV ejection time were measured and averaged over 10 consecutive cycles, as previously described.[15]

Blinding and reproducibility: Both the echocardiographic variables and the systolic time intervals were measured blindly: the recordings of the alcoholic subjects were mixed up with those of the control subjects (see below), coded and analyzed by an investigator (PK) other than the one who had performed the examinations (MK). The reproducibility of these methods in our hands has been validated previously.[13,15]

Control subjects: For a control group, we studied 34 male volunteers aged 27 to 59 years (mean 40). All were only infrequent or moderate drinkers and free of cardiovascular, metabolic and respiratory diseases, according to history, physical examination and 12-lead electrocardiography. They underwent an echocardiographic LV study and determination of the systolic time intervals as previously described. The ultrasound recordings were of acceptable quality in all 34 subjects. Tracings for the systolic time intervals were of acceptable quality in 29.

Statistical analysis: Differences in the LV measurements between the alcoholic and control groups were assessed by Student's *t* test and analysis of covariance; p values <0.05 were considered statistically significant. Multiple linear regression was used to examine, among the alcoholics, the dependence of the LV size, mass and function on the details of the drinking history and on possible confounding factors. Grossly skewed data were log-transformed before fitting them into the regression equations. The models were assessed by the F test on their overall significance, by 2-tailed *t* tests on the estimated coefficients and by the R^2 statistic. Selected univariate regression curves were also computed without presupposing the shape of the function. For this purpose we used the locally weighted scatterplot smoother developed by Cleveland[16] and available in Systat-Sygraph software.[17] This method produces a regression curve by running along the x values and finding predicted values from a weighted average of nearby y values. We chose a running window that included 90% of the data points.

TABLE I Summary of the Drinking Histories in Alcoholics

	Mean	Median	Range
Total duration of heavy drinking (yr)	13	13	1–25
Length of the last drinking period (wk)	28	8	1–250
Daily ethanol consumption (g)	294	300	90–690
Recent ethanol exposure* (g/kg)	658	283	9–3,990
Duration of abstinence (days)	9	7	1–55

* Length of the last drinking period × 7 × daily ethanol consumption/body weight.

RESULTS

Descriptive data on the alcoholics: All alcoholics were episodic drinkers; their drinking histories are summarized in Table I. Quantitative smoking data were available in 70 alcoholics: 11 were nonsmokers and the mean cigarette consumption in the remainder was 24/day (median 20; range 5 to 60). All except 1 alcoholic had a blood hemoglobin concentration >120 g/liter. At least 1 of the measured liver enzymes was elevated in 45 alcoholics (58%) and all 3 in 13 (17%). None had a history or signs of liver cirrhosis. Serum postassium and magnesium were each abnormally low in 2 alcoholics. The electrocardiogram revealed a voltage sum ≥ 35 mm in 19 alcoholics (26%) of whom 6 were aged >40 years. The radiologic heart volume was >500 ml/m^2 of body area (the upper limit of normal in our laboratory) in 20 alcoholics (29%) but >600 ml/m^2 in only 1 (2%). None had pulmonary venous congestion.

Comparisons of alcoholics and control subjects: Table II summarizes the data on heart rate, blood pressure and the LV measurements in the alcoholic and control subjects. The between-group differences found in the LV end-systolic diameter index, posterior wall thickness, mass index and systolic time interval ratio remained statistically significant (p <0.05) even after adjustment for different heart rates by analysis of covariance.

Multiple linear regression analyses: Linear regression models were fitted to the data of the alcoholics using the duration of chronic heavy drinking, log recent ethanol consumption, duration of abstinence, daily cigarette consumption, age and systolic blood pressure as independent (explanatory) variables and the LV measurements (end-diastolic diameter index, end-systolic diameter index, fractional shortening, peak diameter lengthening rate, posterior wall thickness, mass index, preejection period and preejection period/ejection time ratio), each in turn as the dependent variable. The duration of chronic heavy drinking had a statistically significant but weak effect on the posterior wall thickness

TABLE II Heart Rate, Blood Pressure and Left Ventricular Measurements in Alcoholic and Control Subjects

Measurement	Alcoholics (n = 78)*	Controls (n = 34)†	p Value‡
Heart rate (beats/min)	68 ± 1	62 ± 2	0.008
Systolic blood pressure (mm Hg)	120 ± 2	121 ± 2	0.860
Diastolic blood pressure (mm Hg)	78 ± 1	77 ± 1	0.659
Left ventricular			
End-diastolic diameter index (mm/m²)	26 ± 0.3	25 ± 0.4	0.120
End-systolic diameter index (mm/m²)	18 ± 0.3	17 ± 0.3	0.019
Fractional shortening (%)	30 ± 0.7	32 ± 0.7	0.057
Peak diameter lengthening rate (mm/s)	121 ± 5	126 ± 5	0.450
Posterior wall thickness (mm)	11 ± 0.2	10 ± 0.2	0.017
Mass index (g/m²)	85 ± 2	77 ± 2	0.001
Preejection period (ms)	100 ± 2	100 ± 2	0.945
Preejection period/ejection time	0.36 ± 0.01	0.33 ± 0.01	0.002

Data are mean ± standard error.

* For echocardiographic measurements, n = 68, and for systolic time intervals, n = 66.

† For systolic time intervals, n = 29

‡ p value from Student's *t* test.

(standardized coefficient 0.36, p = 0.01) but not on the other measurements, and neither log recent ethanol consumption nor the duration of abstinence were significantly related to the LV measurements. Smoking had a direct effect on both the end-systolic diameter index (standardized coefficient 0.38, p = 0.01) and the preejection period (standardized coefficient 0.39, p = 0.01), and age had a negative effect on the peak diameter lengthening rate (standardized coefficient −0.29, p = 0.03). The regression model was statistically significant for the LV end-systolic diameter index (F = 2.35, R^2 = 0.22, p = 0.04), peak diameter lengthening rate (F = 2.37, R^2 = 0.25, p = 0.04), posterior wall thickness (F = 2.53, R^2 = 0.23, p = 0.03) and preejection period (F = 2.71, R^2 = 0.27, p = 0.02). Even the overall fits were thus relatively poor, and generally <25% of the variation in the LV measurements could be attributed to the combined effect of the aforementioned explanatory factors.

Nonlinear univariate regressions: Because the hypothesis of linear associations between the drinking history and the LV measurements had to be largely rejected, we computed univariate regression curves between selected LV measurements and the duration of heavy drinking or the quantity of recent ethanol use, without making any assumptions about the shape of the function between each 2 variables (Figures 1 to 4).

DISCUSSION

We found that, even though alcoholics as a group had an increased mass and impaired systolic function of the left ventricle, there was no simple relation between the degree of these abnormalities and either the total duration of heavy drinking or the quantity of the most

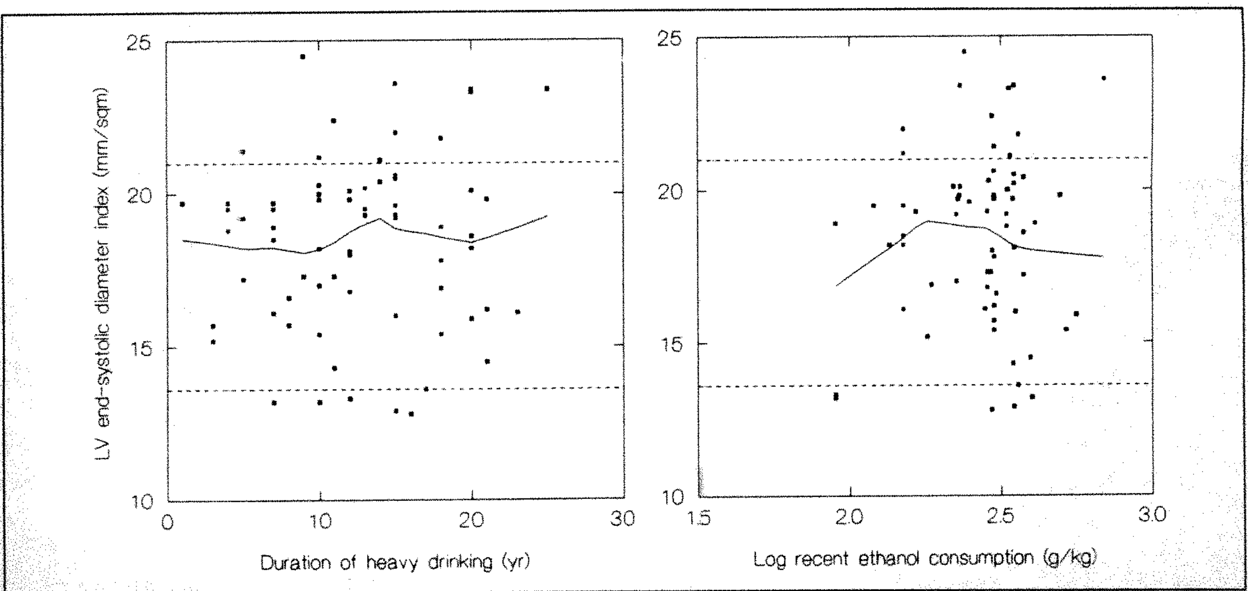

FIGURE 1. Left ventricular (LV) end-systolic diameter index in relation to the duration of heavy drinking and the quantity of recent ethanol consumption in 68 chronic alcoholics. ***Solid lines*** **represent the regression curves computed by the locally weighted scatterplot smoother of Cleveland.[16]** ***Dashed horizontal lines*** **indicate the upper and lower 95% confidence intervals for the left ventricular measurements in 34 healthy control subjects.**

recent ethanol exposure. Although posterior wall thickness was statistically significantly related to the duration of heavy drinking, even this association was weak and explained only about 13% of the variation in wall thickness. In all, our data thus attest against any important linear association between the severity of self-reported alcohol abuse and the degree of LV hypertrophy and dysfunction in chronic alcoholics.

Comparison with earlier investigations: Our main observations are in reasonable harmony with 2 different sets of earlier data.[2,3] Askanas et al[2] examined 73 noncardiac alcoholics by echocardiography and systolic time intervals and found no differences in LV mass or systolic function between alcoholics with drinking histories <15 or ≥15 years. They did not, however, take into account the quantity of daily consumption. Kino et al[3] reported no obvious differences in LV size, mass or performance between 22 alcoholics drinking >125 ml/day of ethanol and 12 alcoholics drinking less, but these investigators ignored the effect of the duration of alcoholism. Neither study adjusted their analyses for other potential determinants of the LV measurements, such as age, blood pressure, smoking and the duration of abstinence.[18-20]

Recently, Urbano-Marquez et al[5] reported that "total lifetime consumption of ethanol" was directly and linearly related to the LV mass and fractional shortening on echocardiography (r = 0.42 and −0.35, respectively) and to the ejection fraction on radionuclide angiography (r = −0.46) in a group of 50 chronic al-

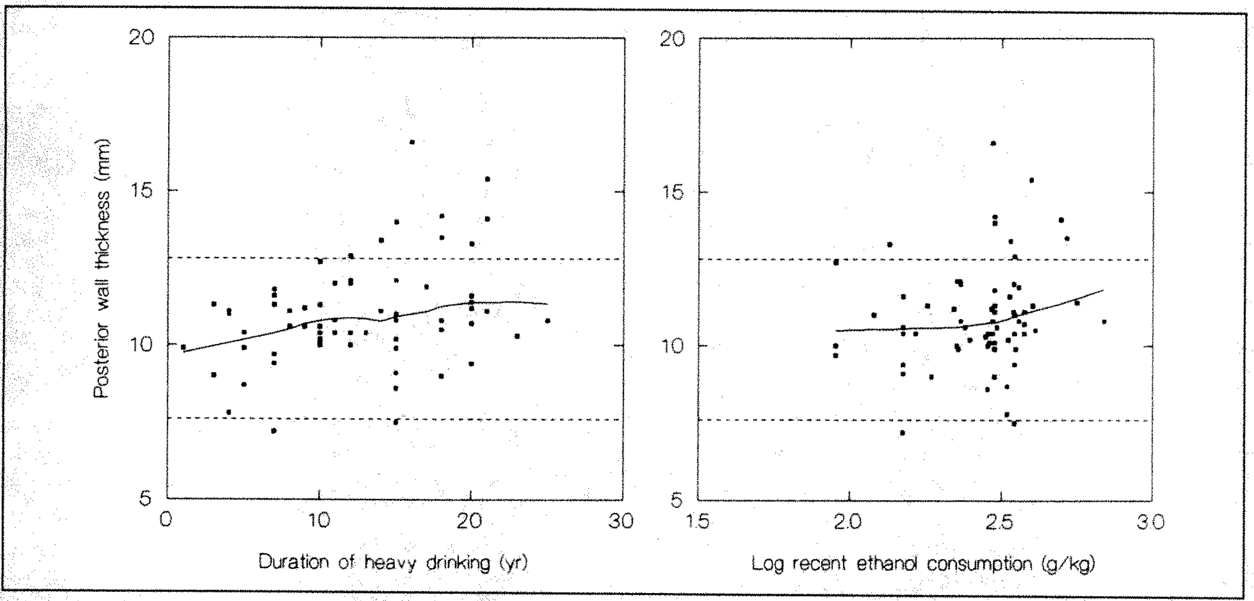

FIGURE 2. Posterior wall thickness in relation to the duration of heavy drinking and the quantity of recent ethanol use in alcoholics. For details, see Figure 1.

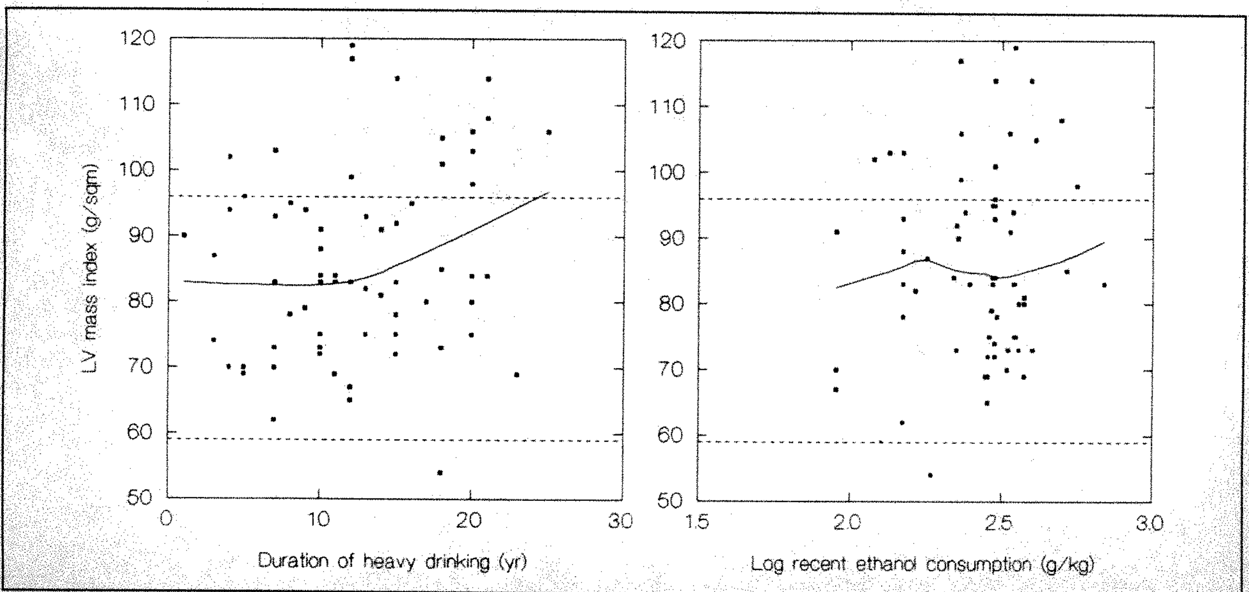

FIGURE 3. Left ventricular (LV) mass index in relation to the duration of heavy drinking and the quantity of recent ethanol use in alcoholics. For details, see Figure 1.

coholics. Although the regressions were statistically significant, the data plots demonstrate that the fits of the linear models were clearly not the best possible (Figures 5 and 6 of the article[5]). To us it seems that the LV measurements were unrelated to ethanol use up to its cumulative dose of about 20 kg/kg of body weight, and only beyond that (in a minority of the study population) did the ejection fraction decrease and the LV mass increase with increasing lifetime consumption. In our own study, the computed regression curves between the LV mass index or the preejection period/ejection time ratio and the duration of heavy drinking were close to horizontal up to about 12 years of heavy drinking but indicated thereafter a steady progression of LV hypertrophy and systolic dysfunction with increasing duration of heavy consumption (Figures 3 and 4). Though inconclusive, these analyses suggest, together with the data of Urbano-Marquez et al,[5] a curvilinear relation between LV involvement and the total duration of alcohol abuse. There might thus exist a threshold in the cumulative ethanol exposure (20 kg/kg of body weight or approximately 12 years of heavy drinking?) beyond which continued abuse would result in a steeper progression of LV involvement.

Factors modifying the relations between left ventricular measurements and history of alcohol abuse: Alcoholics are notoriously unreliable in their drinking histories, at least at routine clinical examination. Although this is a possible confounding factor, it should be noted that alcoholism was in our study a known and "accepted" condition, and the subjects therefore had little reason to keep their true drinking habits from the examiner. The cross-sectional design of our study is another potential limitation because, assuming that the alcoholic heart muscle disease has prognostic influence, it could cause a bias toward studying proportionally less severe involvement with increasing duration and severity of alcoholism. This in turn could weaken the association of the LV measurements with any index of the severity of heavy drinking. This theoretical shortcoming likewise concerns each of the comparable studies done hitherto.[2,3,5]

But is it realistic to expect a simple linear dose-injury relation for the long-term cardiotoxicity of ethanol? The basic mechanisms and course of alcoholic heart muscle injury are still poorly understood, even to the point that there is debate as to whether congestive alcoholic cardiomyopathy represents a disease entity in its own right. Studies in adult animals have uniformly failed to produce dilated congestive LV failure by chronic ethanol administration, and although subtle biochemical, structural and functional abnormalities are common, no simple dose-injury relation has been described.[21-23] Furthermore, only a small minority of chronic human alcoholics (probably less than 5%)[24] ever develop clinical evidence of LV dysfunction, which suggests that there must be either individual sensitivity to the cardiotoxicity of alcohol or noxious co-factors involved in the more severe cases. Hypertension, malnutrition, intercurrent viral myocarditis, smoking and immunologic disorders have been incriminated as co-factors, but none has so far proved to be of current importance.[21,25] Incidentally, smoking seemed to have an independent negative influence on LV systolic function in our study: the more cigarettes the alcoholic consumed daily, the larger was the LV end-systolic size and the longer the preejection period. This conforms with earlier data showing smoking-related LV impairment in humans[19] and in experimental animals.[26] An interaction of smoking with ethanol on myocardium, however, has not been detected.[27]

Finally, we would like to underscore that our data did show an undisputable LV involvement in the form of hypertrophy and mild systolic dysfunction in asymp-

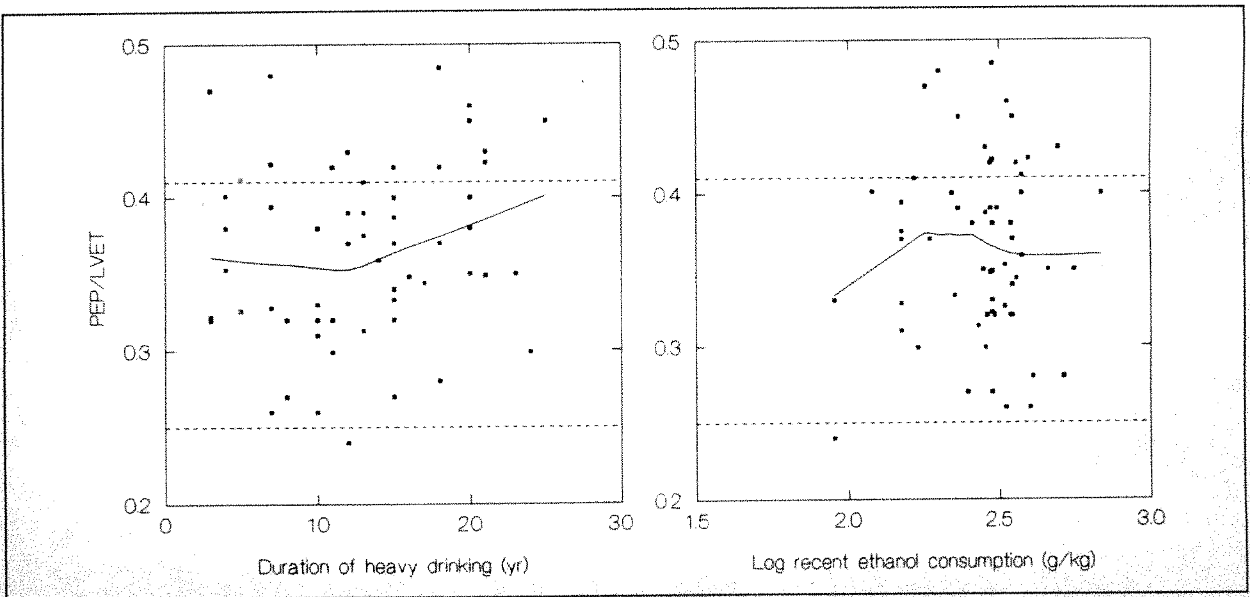

FIGURE 4. Preejection period/left ventricular ejection time (PEP/LVET) ratio in relation to the duration of heavy drinking and the quantity of recent ethanol use in alcoholics. For details, see Figure 1.

tomatic alcoholics, even though we failed to find any distinct model for the association of these changes with the duration and quantity of alcohol abuse. More research is needed to uncover the determinants of the severity of heart muscle disease in alcoholics and the mechanisms of the eventual development of clinical dysfunction. Ethanol may not be the only culprit.

Acknowledgment: We thank Kalevi Laitinen, MD, Matti Välimäki, MD, and Reino Ylikahri, MD (deceased in April 1990), for helping us recruit the alcoholics.

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Hemodynamic and Electrophysiologic Evaluation of Patients with Hypertrophic Cardiomyopathy Surviving Cardiac Arrest

Lameh Fananapazir, MD, and Stephen E. Epstein, MD

Hemodynamic and electrophysiologic studies were performed in 30 survivors of sudden cardiac arrest with hypertrophic cardiomyopathy (HC) to determine responsible factors. Electrophysiologic abnormalities alone were present in 27 patients (90%): sinus node dysfunction in 14 (47%), delayed atrioventricular nodal conduction in 1 (3%), abnormal His-Purkinje conduction in 7 (23%), an inducible atrial tachycardia in 7 (23%), and inducible sustained ventricular arrhythmia in 21 (70%). Sustained ventricular arrhythmia was polymorphic ventricular tachycardia (VT) in 18 patients (86%), monomorphic VT in 2 patients (7%) and ventricular fibrillation in 1 patient (3%). In 1 patient the arrhythmia recorded during an episode of cardiac arrest and induced at electrophysiologic study was polymorphic VT. VT was induced with ≤ 2 extrastimuli in only 1 patient (3%) but with ≤ 3 extrastimuli in 20 patients (97%).

Potential causes of sudden cardiac arrest were found in all patients and were multiple in 13 patients (43%). These were (1) ventricular electrical instability in 21 patients (70%), (2) severe left ventricular outflow tract obstruction in 8 patients (27%), (3) bradycardia in 5 patients (17%), (4) myocardial ischemia associated with hypotension in 5 patients (17%), and (5) atrial tachycardia resulting in hypotension in 4 patients (13%).

Of the 21 patients with inducible sustained ventricular arrhythmia, 17 received an implantable defibrillator device and 4 were treated with antiarrhythmic drugs. Seven patients underwent left ventricular septal myectomy. Three patients with atrial tachycardia received antiarrhythmic medication. One patient had catheter ablation of a concealed posteroseptal accessory pathway. Three patients with myocardial ischemia as the only abnormality were treated with verapamil and propranolol (2 also received implantable defibrillators).

During a mean follow-up period of 18 ± 19 months (maximum 75), 4 patients died suddenly and 4 patients received a total of 13 defibrillator shocks (1-year survival rate of 93% and a 1-year event-free rate of 80%).

Thus, electrophysiologic studies identify potential mechanisms for cardiac arrest in most patients with HC. Although most cardiac arrest survivors with HC have an inducible sustained VT and may benefit from an implantable defibrillator, hemodynamic plus hemodynamic studies in many patients identify other potential etiologic or aggravating factors that may also require treatment.

(Am J Cardiol 1991;67:280–287)

Approximately 50% of sudden cardiac arrest survivors with hypertrophic cardiomyopathy (HC) are dead or have further cardiac arrest within 5 years after the initial episode.[1] Attempts to reduce the incidence of sudden death in these patients requires an understanding of the mechanisms that may be responsible for this devastating complication.

Electrophysiologic studies have an established role in the management of survivors of sudden cardiac arrest who have cardiac diseases other than HC.[2] Although a variety of electrophysiologic abnormalities have been described in small numbers of patients with HC,[3–9] the ability of these studies to elucidate the mechanisms responsible for cardiac arrest, and whether such studies will result in practical and effective therapeutic strategies for survivors of sudden cardiac arrest with HC, remain unclear. The present investigation documents the Holter, electrophysiologic and hemodynamic abnormalities in 30 patients with HC who were successfully resuscitated from a cardiac arrest, and determines the frequency with which these tests reveal abnormalities that are amenable to therapy.

METHODS

Patient group (Table I): The patient group consisted of 30 consecutive patients with HC who presented with sudden cardiac arrest between February 1984 and January 1990. Their ages were 39 ± 20 years (range 7 to 72 years). Five patients had undergone operation for obstructive HC and 5 patients had a family history of sudden death. Sudden cardiac arrest was defined as a history of cardiopulmonary resuscitation that required defibrillation within 1 hour of collapse. HC was defined as nondilated and hypertrophied left ventricle, in the absence of another cardiac or systemic disease that could produce left ventricular hypertrophy. All patients un-

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TABLE I Clinical Characteristics and Potential Causes of Cardiac Arrest in Patients with Hypertrophic Cardiomyopathy

Pt. No.	Age (yr) & Sex	LVOT Obstruction	Tachycardia-Induced MI	Bradycardia		Inducible Arrhythmia	
				SND	His-P	SVT	VA
1	21F	+	0	0	0	0	MVT
2	72F	+	0	0	0	0	MVT
3	64M	+	0	0	0	0	PVT
4	32M	+	0	0	0	0	PVT
5	54M	+	0	0	0	0	PVT
6	68F	+	0	0	0	0	PVT
7	56M	+	0	0	0	0	PVT
8	57M	+	0	0	0	0	PVT
9	44M	0	0	0	0	0	PVT
10	11M	0	0	0	0	0	PVT
11	32M	0	0	0	0	0	PVT
12	18M	0	0	0	+	0	PVT
13	49M	0	0	0	+	0	PVT
14	49M	0	0	0	0	0	PVT
15	27F	0	0	0	0	0	PVT
16	61F	0	0	0	0	0	PVT
17	50F	0	0	0	0	0	PVT
18	62M	0	0	0	0	0	VF
19	22M	0	0	0	0	0	PVT
20	15M	0	+	+	0	0	PVT
21	18F	0	+	0	0	0	PVT
22	20F	0	+	0	0	0	0
23	7F	0	+	0	0	0	0
24	10M	0	+	0	0	0	0
25	60F	0	0	0	0	ART	0
26	37F	0	0	0	0	ART	0
27	9M	0	0	0	0	ART	0
28	39F	0	0	0	0	AVRT	0
29	65F	+	0	+	0	0	0
30	32F	0	0	+	0	0	0

ART = atrial reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; His-P = His-Purkinje conduction abnormality; LVOT = left ventricular outflow tract; MI = myocardial ischemia; MVT = sustained monomorphic ventricular tachycardia; PVT = sustained polymorphic ventricular tachycardia; SND = sinus node disease; SVT = supraventricular tachycardia; VA = sustained ventricular arrhythmia; VF = ventricular fibrillation; + = present; 0 = absent.

derwent 48-hour Holter monitoring, right- and left-sided cardiac catheterization, coronary arteriography and electrophysiologic studies. All patients had normal coronary arteries. Obstructive HC was defined as basal left ventricular outflow tract gradient of ≥30 mm Hg. Long-term follow-up assessment included 6 monthly visits to the cardiology clinic and telephone interrogation of patients, their relatives and their physicians. Time interval between cardiac arrest and evaluation was 2.5 ± 2.9 months.

Electrophysiologic study: All cardioactive drugs were discontinued ≥5 half-lives before the study. The study was performed after an overnight fast and the patient sedated with 10 mg of diazepam administered orally. All patients gave informed consent. Three multiple electrode catheters (5Fr or 6Fr) were introduced percutaneously into the right femoral vein and positioned under fluoroscopic guidance in the high right atrium, across the tricuspid valve and in the right ventricular apex. In patients with supraventricular tachycardia, an additional quadripolar catheter was placed in the coronary sinus through a subclavian vein. After assessment of supraventricular function, the high right atrial catheter was repositioned in the right ventricular outflow tract for ventricular stimulation. The right femoral artery was cannulated (8Fr sheath) for continuous recording of the systemic arterial pressure and for left ventricular stimulation. Intracardiac electrograms were filtered at 30 to 500 Hz and standard electrocardiographic leads I, II and V_1 were filtered at 0.1 to 20 Hz and displayed simultaneously on a multichannel oscilloscope (Electronics for Medicine, VR16) and recorded on light-sensitive at a paper speed of 100 mm/s. The 12-lead electrocardiogram was recorded during induced arrhythmia. Programmed stimulation was performed using a digital programmable stimulator (Bloom Associates) and 2.0-ms rectangular pulses at twice late diastolic threshold.

Details of our programmed stimulation protocol have been described previously.[10] Briefly, the following were determined: sinus node recovery time, sinoatrial conduction time, atrial refractory periods, atrioventricular nodal refractory periods, Wenckebach cycle length, shortest cycle length with 1:1 atrioventricular nodal conduction, site and characteristics of any existing atrioventricular accessory pathway, ventricular refractory periods, and extrastimuli intervals that failed to induce or resulted in the induction of a sustained ventricular arrhythmia. Programmed ventricular stimulation involved a stepwise increase in aggressiveness: (1) insertion of 1 (S_2), 2 (S_3) and 3 (S_4) extrastimuli into normal sinus rhythm at the right ventricular apex; (2) introduction of S_2 and S_3 after three 8-beat ventricular drives (S_1) at cycle lengths of 600, 500 and 400 ms, first at the right ventricular apex, and second at the right ventricular outflow tract; (3) insertion of S_2, S_3 and S_4 after the three S_1 drives, first at the right ventricular site, and second at the right ventricular outflow tract site; and (4) insertion of S_2, S_3 and S_4 after the three S_1 drives at a left ventricular site. The coupling intervals were reduced to refractoriness. The end point of programmed stimulation was ventricular refractoriness or induction of a sustained ventricular arrhythmia. The stimulation protocol did not include ventricular burst pacing or Isuprel® infusion.

Definitions: Nonsustained ventricular tachycardia (VT) was VT of 3 beats to ≤30 seconds' duration that terminated spontaneously. Sustained VT was VT of >30 seconds' duration or VT requiring termination due to hypotension. VT with continuously changing QRS morphology was termed polymorphic and that with constant QRS morphology was termed monomorphic. Ventricular fibrillation was ventricular arrhythmia without discernable discrete beats identifiable on the surface 12-lead electrocardiogram and with continuous intracardiac electrical activity. An appropriate defibrillator shock was defined as an electric discharge by the device that was preceded by syncope.

Statistical analysis: Data are expressed as mean ± 1 standard deviation unless otherwise specified. The Student's *t* test was used for comparison of data. Cumulative survival was determined by product-limit survival analysis using sudden death and defibrillator shocks as time variables. A p value <0.05 was considered significant.

RESULTS

Left ventricular outflow tract obstruction: Eight patients had significant basal left ventricular outflow tract gradients: 88 ± 27 mm Hg, range 50 to 130 mm Hg.

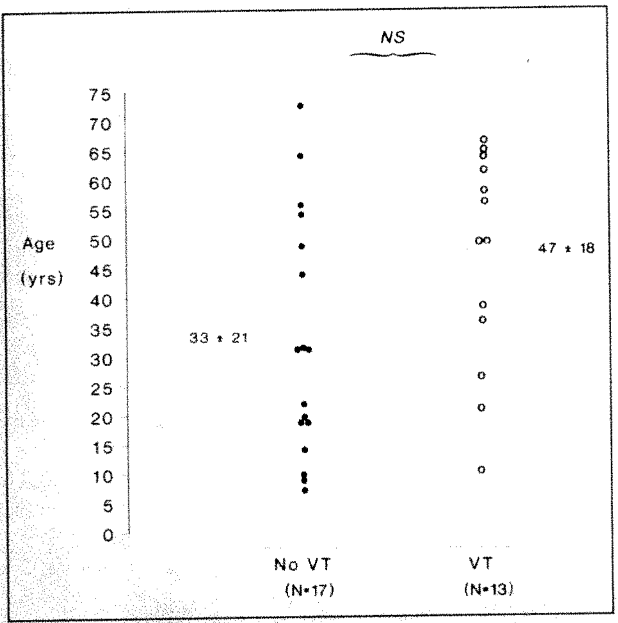

FIGURE 1. Comparison of the age distributions of sudden cardiac arrest survivors with and without ventricular tachycardia (VT) during 24- to 48-hour Holter monitoring. NS = not significant.

Prevalence of spontaneous nonsustained ventricular tachycardia during Holter monitoring and its relation to inducibility of sustained ventricular arrhythmia: Only 13 patients (39%) had nonsustained VT during Holter monitoring (Figure 1): 1 of 8 patients (13%) aged ≤20 years and only 10 of 19 patients (53%) ≥30 years had VT. The mean ages of patients with and without VT during Holter monitoring were not significantly different (Figure 1). Five of 17 patients (29%) without VT during Holter monitoring were aged 50 to 72 years. Ten of the 13 patients (77%) with VT during Holter monitoring had an inducible sustained ventricular arrhythmia compared with 11 of 17 patients (65%) without VT during Holter monitoring (p >0.05).

Electrophysiologic abnormalities: Electrophysiologic abnormalities were present in 27 patients (90%): sinoatrial conduction time >120 ms in 14 patients (47%) and corrected sinus node recovery time >500 ms in 1 (3%); delayed atrioventricular node conduction (Wenckebach periodicity occurred at drive cycle length of >500 ms) in 1 patient (3%) and rapid atrioventricular nodal conduction (Wenckebach periodicity occurred at a drive cycle length of <300 ms) in 3 patients (10%); His-Purkinje conduction abnormality (HV interval of >55 ms or induction of infra-Hisian block during atrial refractory period measurement or atrial incremental pacing) in 7 patients (23%), inducible atrial fibrillation in 3 patients (10%), atrial reentrant tachycardia in 3 patients (10%), and atrioventricular reentrant tachycardia due to a concealed posteroseptal accessory pathway in 1 patient (3%). Additionally, 23 patients (77%) had an inducible ventricular arrhythmia (sustained in 21).

Induction and characteristics of sustained ventricular arrhythmias: Sustained ventricular arrhythmia was polymorphic VT in 18 patients (86%), monomorphic VT in 2 patients (7%) and ventricular fibrillation in 1 patient (3%). The cycle lengths of the monomorphic VT were 250 and 265 ms, respectively, and cycle lengths of polymorphic VT were 230 ± 22 ms.

Sustained ventricular arrhythmia was induced at the first site (right ventricular apex) in 7 patients (33%), second site (right ventricular outflow tract) in 7 patients (33%), and at the third site (left ventricle) in 7 patients (33%). Sustained VT (polymorphic) was induced with 2 extrastimuli in only 1 patient (3%) with an S_1, S_2 and S_3 of 400, 270 and 210 ms but required 3 extrastimuli in the remaining 20 patients (97%). The premature intervals that resulted in induction of monomorphic VT were: S_1, 600 ms; S_2, 270 ms; S_3, 200 ms; and S_4, 220 ms, and S_1, 600 ms; S_2, 280 ms; S_3, 250 ms; and S_4, 220 ms. The premature intervals that induced polymorphic VT were: S_1, 470 ± 95 ms; S_2, 278 ± 24 ms; S_3, 228 ± 24 ms; and S_4, 219 ± 20 ms. The S_1, S_2, S_3 and S_4 intervals that failed to induce sustained ventricular arrhythmia (n = 9) were not significantly different: S_1, 400 ms; S_2, 280 ± 29 ms; S_3, 246 ± 23 ms; and S_4, 212 ± 29 ms. All episodes of induced sustained VT required rapid termination due to hypotension. A single direct-current shock of 200 J was successful in all cases.

Potential mechanisms of sudden cardiac arrest and therapy: Several potential mechanisms for sudden cardiac arrest were identified. In 13 patients (43%) these mechanisms were multiple. Their prevalence and management were as follows:

VENTRICULAR ELECTRICAL INSTABILITY: Twenty-one patients had an inducible sustained ventricular arrhythmia; in 18 patients the ventricular arrhythmia was polymorphic VT. The importance of polymorphic VT was underlined by the recording of this arrhythmia during a second episode of cardiac arrest that occurred in the hospital in a patient (32-year-old man) who had presented 2 weeks earlier with a sudden cardiac arrest (Figure 2, top). Both episodes were unheralded by premonitory symptoms and had occurred while the patient was standing. Before the cardiac arrest the patient had also been free of cardiac symptoms. Prompt resuscitation on both occasions resulted in full recovery. Cardiac enzymes were not elevated and no arrhythmia was recorded during 3 weeks of telemetry and 4 days of Holter monitoring. Cardiac catheterization showed a basal left ventricular outflow tract gradient of 100 mm Hg. Coronary angiography was normal. At electrophysiologic study, polymorphic VT was induced at a left ventricular site using 3 extrastimuli at S_1, S_2, S_3 and S_4 intervals of 500, 260, 240 and 220 ms (Figure 2, bottom). Polymorphic VT was also the arrhythmia induced during epicardial stimulation at the time of operation. The first 5 patients with inducible sustained ventricular arrhythmia were treated with antiarrhythmic medications. Three of these patients died subsequently, 2 receiving amiodarone therapy. The remaining 16 patients received an implantable defibrillator device.

SEVERE LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION: Nine patients had significant basal left ventricular outflow tract obstruction. However, all 9 patients had other potential mechanisms for sudden cardiac arrest: 8 patients had an inducible sustained VT and 1 patient had abnormal His-Purkinje conduction and sinus pauses that resulted in syncope. The 8 patients with inducible VT underwent septal myectomy and implantation of a defibrillator device. The remaining patients with sinoatrial and distal conduction disease received a dual chamber permanent pacing device. After pacemaker implantation, the left ventricular outflow tract gradient was insignificant owing to echocardiographically demonstrated pacing-induced paradoxical septal motion. Thus, this patient did not undergo septal myectomy.

BRADYCARDIA: Although the sinus node was abnormal in about half of the patients, in only 3 patients did sinus bradycardia and pauses result in presyncope or syncope. In 2 of the 3 patients, symptomatic sinus node disease was associated with other mechanisms that could cause sudden cardiac arrest, but in 1 patient sinus node disease was the only detected abnormality. Similarly, although the HV interval was prolonged in about one-fourth of the patients, block distal to the His bundle was induced in only 2 patients. All 5 patients received permanent pacemakers.

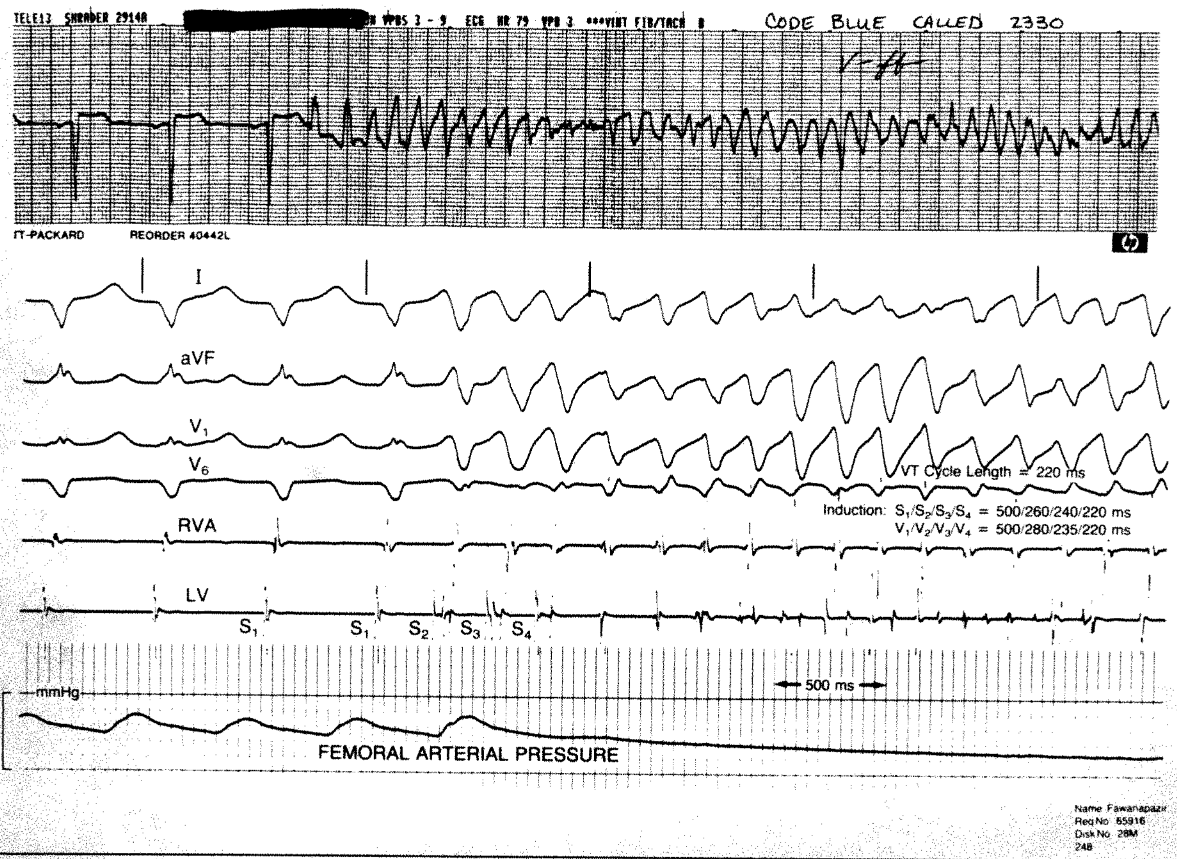
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FIGURE 2. ***Top,*** **telemetry recording of polymorphic ventricular tachycardia causing cardiac arrest in a patient (DS) with a history of similar presentation 2 weeks earlier.** ***Bottom,*** **induction of polymorphic ventricular tachycardia in a sudden cardiac arrest survivor (DS) in whom the same arrhythmia had been shown to be responsible for the cardiac arrest.**

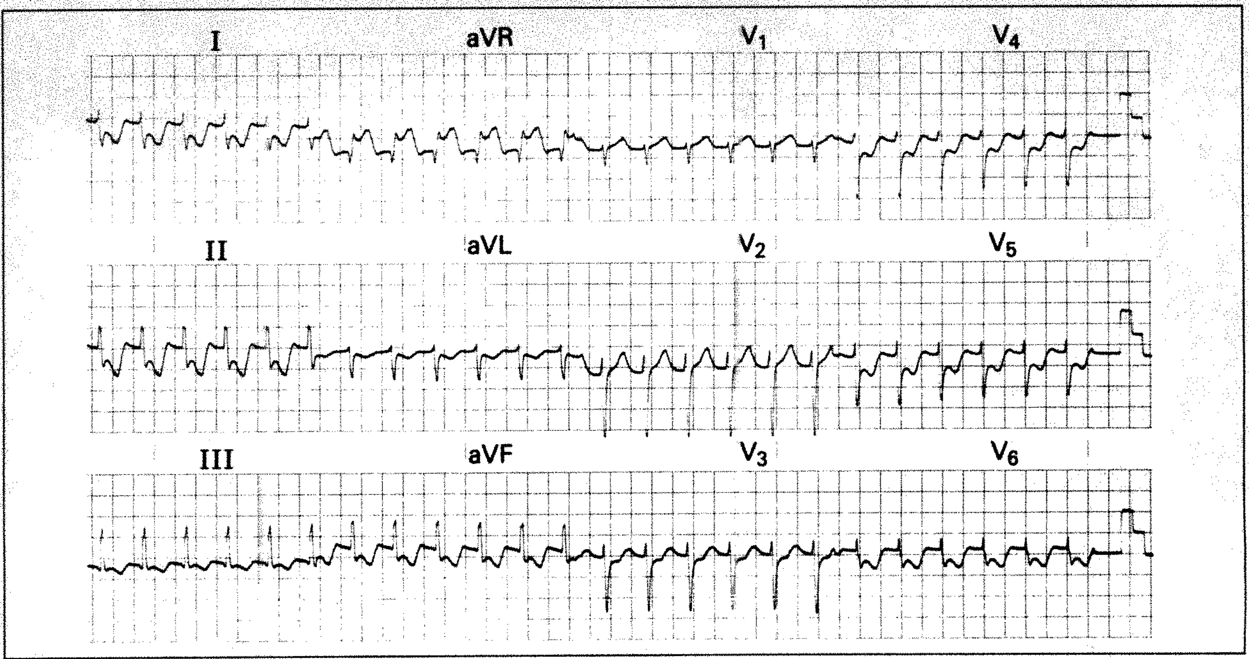

FIGURE 3. Twelve-lead electrocardiogram recorded during right atrial pacing at a rate of 145 beats/min showing marked (≥7 mm) widespread ST depression in sudden cardiac arrest survivor (DH) with nonobstructive hypertrophic cardiomyopathy and normal electrophysiologic findings.

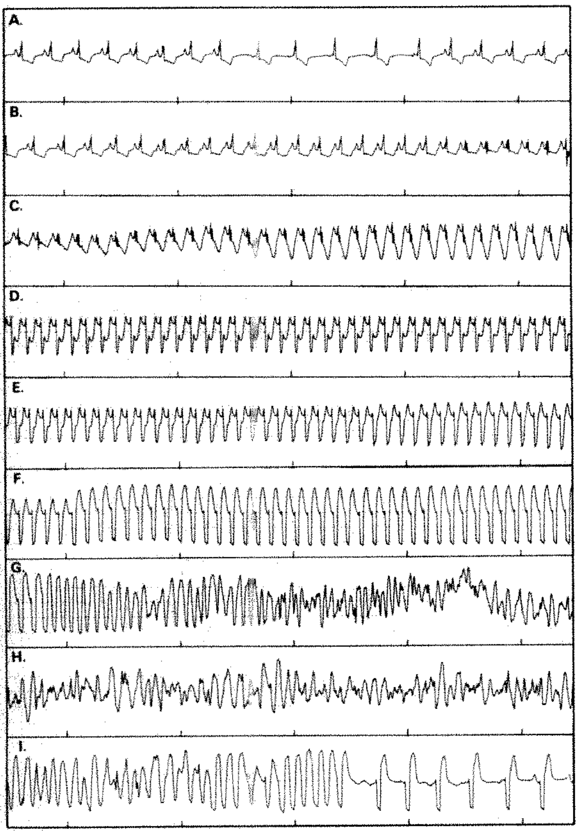

FIGURE 4. Holter recording of events leading to syncope in a patient (AR, aged 7 years) with nonobstructive hypertrophic cardiomyopathy who had numerous episodes of witnessed syncope and cardiac arrest. An increase in heart rate results in marked ST depression and progressive widening of the QRS complex. The episode results in ventricular fibrillation that terminates spontaneously (*panels A to D* are continuous). The abrupt widening of the QRS was reproduced during atrial pacing and shown to be related to conduction abnormality (Figure 5). No arrhythmias were induced during programmed ventricular stimulation.

MYOCARDIAL ISCHEMIA ASSOCIATED WITH HYPOTENSION: Five patients with nonobstructive HC had myocardial ischemia that was precipitated by modest increases in heart rates and associated with severe hypotension. Two of the 5 patients also had an inducible sustained VT. All 5 patients developed marked electrocardiographic ischemic changes and profound hypotension in response to right atrial pacing at rates >130 beats/min (Figure 3). In 1 patient with frequent episodes of syncope and cardiac arrest, Holter monitoring during a syncopal episode showed a rapid narrow complex regular tachycardia that altered its morphology abruptly to a wide complex tachycardia and then degenerated into ventricular fibrillation. At the electrophysiologic study, atrial pacing at rates >120 beats/min induced profound hypotension and ST-segment depression, associated with similar alteration in QRS morphology and marked increase in the HV interval (Figures 4 and 5). No arrhythmias were induced by programmed ventricular stimulation. We concluded that the rapid heart rate induced severe myocardial ischemia and hypotension that resulted in aberrant conduction and ventricular fibrillation. All 5 patients had 2 to 10 mm of ST depression during treadmill exercise. Thallium scans revealed widespread exercise-induced myocardial perfusion defects that improved with verapamil and reversed during the period after exercise in all 5 patients (Figure 6). Only 1 of the 5 patients had chest discomfort during ischemic episodes. All 5 patients were treated with verapamil[11] and propranolol. Four patients also received the defibrillator device.

SUPRAVENTRICULAR ARRHYTHMIA RESULTING IN SEVERE HYPOTENSION: Two patients had paroxysmal and inducible atrial fibrillation (induced during atrial premature stimulation). Atrial fibrillation was well tolerated hemodynamically. Both patients were treated with procainamide but also received defibrillators for induci-

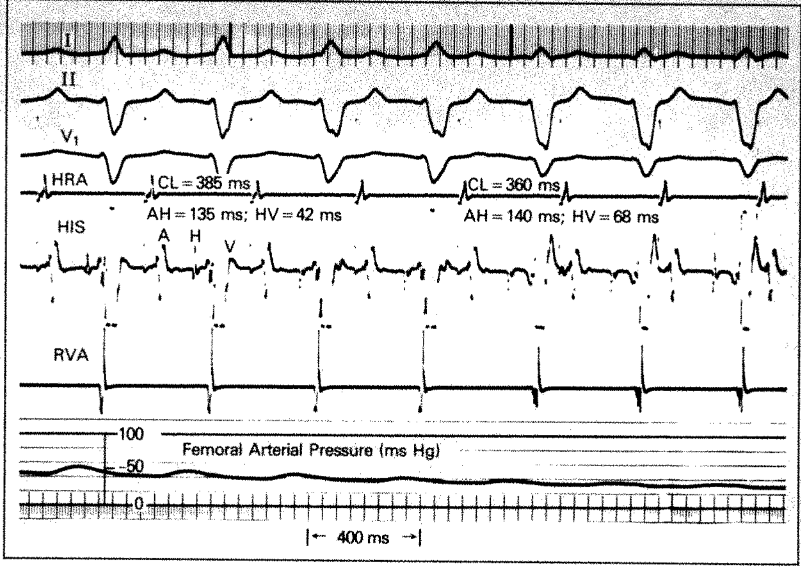

FIGURE 5. Right atrial pacing in patient AR resulted in profound hypotension and reproduced the ST depression and widening of the QRS complex seen during spontaneous episodes of sinus tachycardia. These changes were associated with progressive prolongation of the HV interval. HRA = high right atrium; RVA = right ventricular apex.

ble sustained VT. A sustained atrial tachycardia, resulting in prompt and marked hypotension, was reproducibly induced in 3 patients during atrial premature stimulation. In all 3 patients, the resulting hypotension probably triggered the cardiac arrest. In 1 of the 3 patients the atrial tachycardia was also induced during programmed ventricular stimulation (Figure 7). This patient had frequent episodes of nonsustained VT during Holter monitoring that may have induced the atrial tachycardia spontaneously. Despite the Holter findings, programmed ventricular stimulation in this patient did not induce VT. Because the atrial tachycardia was not recorded during Holter monitoring but only induced by programmed atrial stimulation, the arrhythmia was untreated in the first patient who presented in this way. The patient subsequently died suddenly. The remaining 2 patients have been treated with procainamide (n = 1) and amiodarone (n = 1). A fourth patient had an inducible atrioventricular reentrant tachycardia due to a concealed posteroseptal accessory pathway associated with hypotension, which would occasionally degenerate into atrial fibrillation resulting in further hypotension. The arrhythmia was treated with catheter ablation of the accessory pathway.

Long-term follow-up: Four sudden deaths have occurred (1, 2, 22 and 48 months after electrophysiologic study) during a mean follow-up period of 18 ± 19 months (maximum 75). Three of the 4 sudden deaths were in patients with inducible ventricular arrhythmias who were treated with procainamide (n = 1) or amiodarone (n = 2). The only electrophysiologic abnormality detected in the remaining patient with nonobstructive HC was an inducible atrial tachycardia. Four of 18 patients with defibrillators have received a total of 13 shocks. At baseline evaluation, 2 of these patients had an inducible polymorphic VT, 1 patient had evidence of myocardial ischemia and an inducible polymorphic VT, and 1 patient had only myocardial ischemia. The shocks

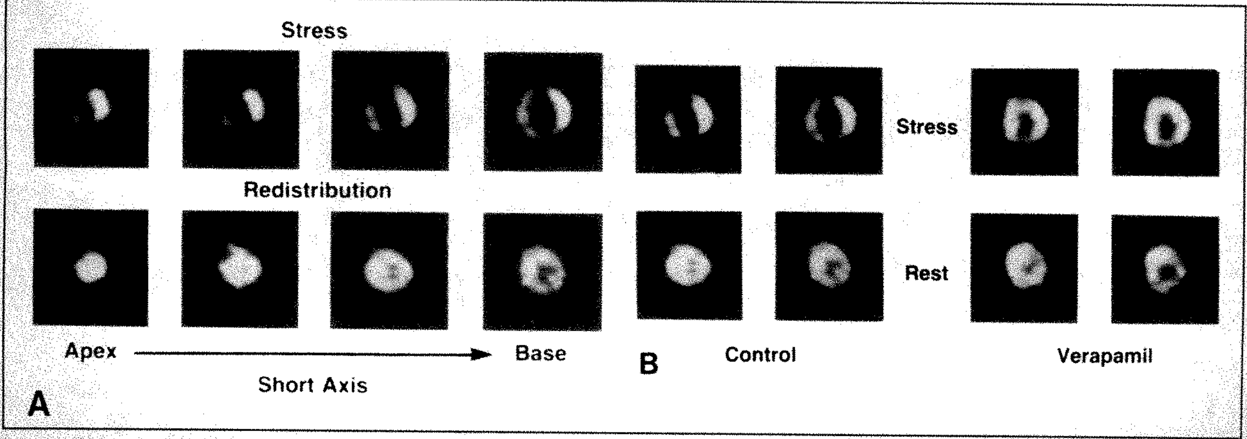

FIGURE 6. *A*, tomographic short-axis thallium-201 perfusion images of the left ventricle in a sudden cardiac arrest survivor with nonobstructive hypertrophic cardiomyopathy, myocardial ischemic electrocardiographic changes associated with hypotension during exercise and atrial pacing, and inducible sustained polymorphic ventricular tachycardia. Under control conditions, there is exercise-induced hypoperfusion of anterior, septal and inferior myocardium, which normalizes on subsequent resting images. *B*, tomographic short-axis thallium-201 perfusion images of the left ventricle (patient illustrated in Figure 5) showing amelioration of the reversible ischemia during exercise by verapamil, 360 mg/day.

occurred 1, 3, 11 and 52 months after electrophysiologic evaluation and defibrillator implantation. The 1-year survival and event- (sudden death or shock) free rates were 93 and 80%, respectively (Figure 8).

DISCUSSION

Previous studies have shown that although VT detected by Holter monitoring identifies a group of HC patients at high risk for sudden death, this rhythm abnormality is not a sensitive predictor of sudden death in young patients.[12,13] Our study confirms this finding; only 1 of 8 sudden cardiac arrest survivors (13%) <20 years of age had VT on Holter. However, our new finding that a large number of older patients also did not have VT during Holter monitoring was of great concern; only 10 of 19 patients (53%) ≥30 years of age had VT on Holter. In contrast to the low sensitivity of VT on Holter in identifying HC patients with cardiac ar-

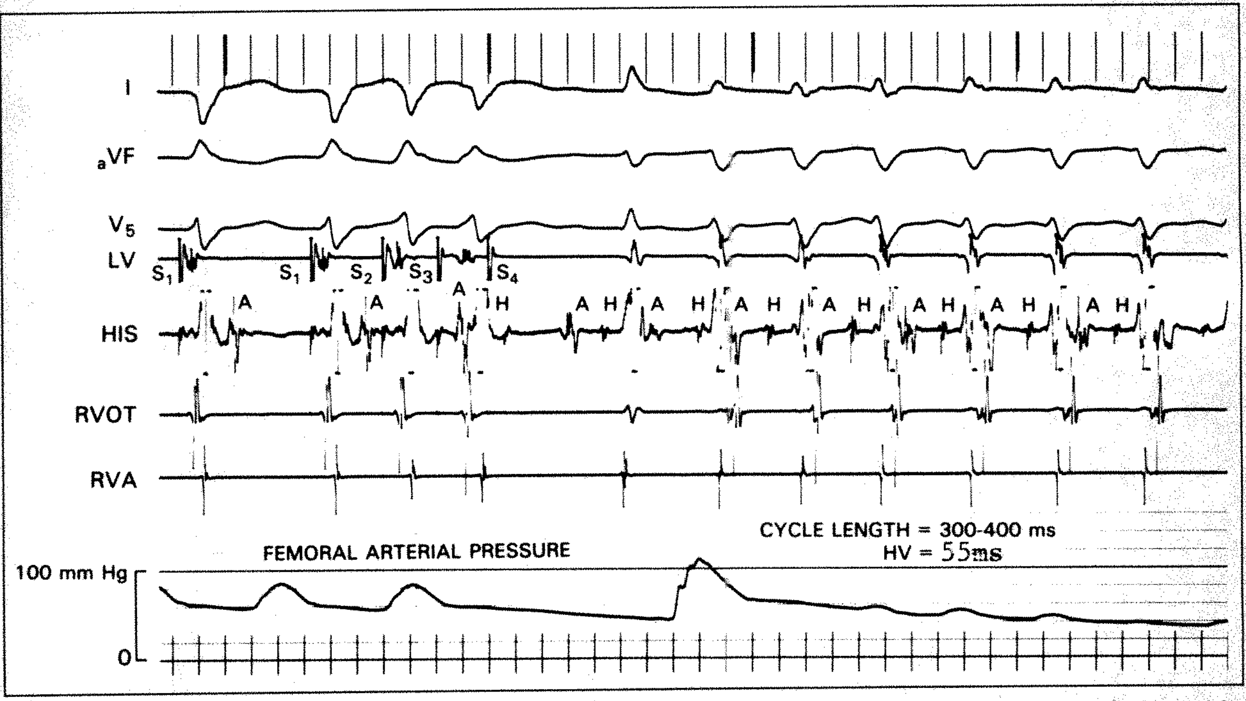

FIGURE 7. Induction of an atrial reentrant tachycardia during programmed ventricular stimulation resulting in marked systemic hypotension in a survivor of sudden cardiac arrest. LV = left ventricle; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

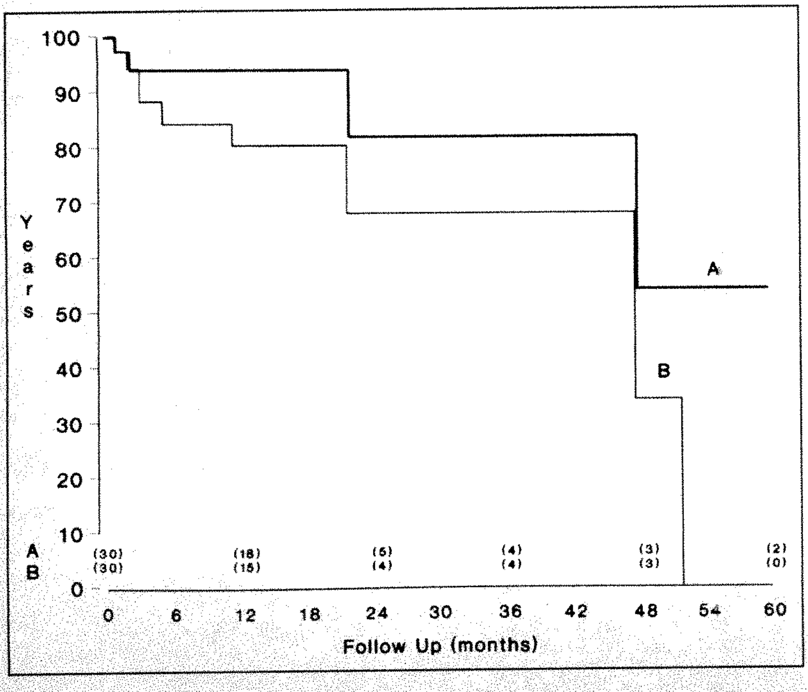

FIGURE 8. Product-limit survival rate (A) and event- (sudden death or defibrillator shock) free rate (B) in the 30 patients with hypertrophic cardiomyopathy who presented with sudden cardiac arrest.

rest, electrophysiologic and hemodynamic studies provided highly reliable information. Thus, in 21 of the 30 survivors (70%) of sudden cardiac arrest, a sustained VT was induced by programmed stimulation. Furthermore, in all the remaining 9 patients without inducible sustained VT, other potential causes of cardiac arrest were identified. This latter finding has important implications. First, it demonstrates the value of electrophysiologic study in identifying the patient at risk of sudden cardiac arrest. Second, it shows that the causes of sudden cardiac arrest in HC are multiple, and that therefore no single therapeutic approach could be effective. Third, it validates the use of our programmed stimulation protocol (3 ventricular sites, 3 drive cycle lengths and 3 extrastimuli) as being both sensitive and specific. For example, a less aggressive stimulation protocol (≤2 extrastimuli) identified substantially fewer sudden cardiac arrest patients who had an inducible sustained VT with the more aggressive stimulation protocol; thus, whereas only 1 of the 21 patients who had no other potential cause of sudden cardiac arrest developed inducible sustained VT with 2 extrastimuli, all 19 patients developed inducible VT with the more aggressive protocol. The fact that the specificity of VT induced by this more aggressive stimulation protocol is not importantly compromised is suggested by the finding that there are patients with sudden cardiac arrest who are not inducible with this protocol, and each of these noninducible patients had another potential cause for sudden cardiac arrest. In addition, in the patient in whom we were fortunate to obtain electrocardiographic recordings of VT during an episode of cardiac arrest, the arrhythmia was induced in the electrophysiology laboratory only from a left ventricular site using 3 extrastimuli. The ventricular arrhythmia most frequently induced in the survivors of cardiac arrest was sustained polymorphic VT. This arrhythmia was induced in 18 of the 21 patients (86%) with inducible ventricular arrhythmia. Monomorphic VT was induced in only 2 patients. We have reported on the significant association between inducibility of sustained polymorphic VT and a history of sudden cardiac arrest or syncope in patients with HC.[10] This arrhythmia in this group of patients is induced with a stimulation protocol that is significantly less aggressive than that used in patients without an inducible ventricular arrhythmia.[10,14] Furthermore, only about 10% of asymptomatic patients have a sustained ventricular arrhythmia induced by our stimulation protocol.[10] The clinical relevance of polymorphic VT is further underlined by the recording of this arrhythmia during the 1 cardiac arrest we witnessed (Figure 2A). This particular patient did not have any VT despite extensive Holter monitoring. As noted, potential causes for cardiac arrest were found by combined electrocardiographic and hemodynamic studies in all patients. Ventricular electrical instability, as shown by inducibility of a sustained VT, was the most frequent finding, present in about two-thirds of patients. In the remaining patients, several other potential causes of cardiac arrest were identified. These included severe left ventricular outflow tract obstruction, myocardial ischemia, sinus node disease, distal conduction disease and atrial arrhythmias. These results indicate that it is only after the specific cause of cardiac arrest in a given patient with HC is identified by combined hemodynamic and electrophysiologic assessment that an effective strategy for the management of sudden cardiac arrest can be devised.

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Uses and Limitations of Transthoracic Echocardiography in the Assessment of Atrial Septal Defect in the Adult

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Two-dimensional and color Doppler echocardiography accurately detected the presence of an atrial septal defect (ASD) in 47 of 50 adults (mean age 40 years) confirmed by surgery or cardiac catheterization, or both. It correctly categorized all patients with ostium secundum and ostium primum ASD but misdiagnosed 3 of 5 patients with surgically proven sinus venosus ASD. The shunt flow volume across the ASD was calculated with the standard Doppler equation, and assuming the ASD to be circular correlated with shunt flow volume obtained by cardiac catheterization (r = 0.74). The maximum width of the color flow signals moving across the ASD was taken as its diameter. Mean flow velocity was determined either by placing a pulsed Doppler sample volume parallel to the flow across the ASD as visualized by color Doppler or by color M-mode examination, which allowed determination of flow velocities using a previously validated method that incorporates a computer analysis of pixel color intensity. The pulmonary to systemic blood flow ratio obtained by color-guided conventional Doppler interrogation of the left and right ventricular outflow tracts correlated poorly with cardiac catheterization results (r = 0.38). In patients with associated tricuspid regurgitation, the peak systolic pulmonary artery pressure obtained by color Doppler-guided continuous-wave Doppler correlated well with that obtained at cardiac catheterization (r = 0.89). The maximum color Doppler jet width of the flow across the ASD poorly correlated with ASD size estimated at surgery (r = 0.50).

(Am J Cardiol 1991;67:288–294)

Atrial septal defects have been visualized by 2-dimensional echocardiography, but false echo "drop-outs" mimicking an atrial septal defect (ASD) are frequently seen in various imaging planes and reduce the specificity of the technique, especially in adults.[1-3] The conventional pulsed and continuous-wave Doppler technique has been used in the quantification of pulmonary to systemic blood flow ratios, but the results have been conflicting, with some investigators demonstrating good correlation with cardiac catheterization and others finding large discrepancies.[4-8] The relatively recently developed technique of color Doppler flow mapping has also been used in the assessment of ASD.[9-11] To date, no large scale studies have been reported demonstrating the usefulness of imaging and Doppler modalities in the assessment of ASD, especially in adults in whom the potential for misdiagnosis is greater than in children who have larger acoustic windows. The present study evaluates the uses and limitations of combined 2-dimensional and conventional and color Doppler echocardiographic modalities in detecting and categorizing the site of ASD and in quantifying shunt volume in 50 adults.

METHODS

Echocardiography: Fifty adults (18 men and 32 women, whose ages ranged from 16 to 76 years [mean 40]) with ASD documented by cardiac catheterization, angiography or surgery, or a combination of these, formed the basis of this study. This group represented all patients with ASD studied by 2-dimensional and conventional and color Doppler echocardiography at our institution who underwent cardiac catheterization (45 patients) or surgery (42 patients). Four patients had associated pulmonary valve stenosis with peak right ventricular systolic pressures of 47, 69, 85 and 109 mm Hg. All these patients underwent color Doppler examinations using either an Aloka, Toshiba, Hewlett-Packard or Advanced Technology Laboratories color flow mapping system. A 2.5-MHz transducer frequency, a frame rate between 15 to 30 frames/s and a pulse repetition frequency varying between 4 and 8 KHz, depending on the examination depth, were used. An attempt was made to examine all the patients using the left precordial, apical, subcostal, suprasternal and right parasternal approaches (Figure 1).[12]

Detection and classification of atrial septal defect: An ASD was diagnosed if a consistent discontinuity in

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the atrial septum was observed in multiple views by 2-dimensional echocardiography or if flow signals were observed by color Doppler, moving from the left atrium into the right atrium through an area of discontinuity in the interatrial septum or through an apparently intact interatrial septum.[5] The ASD was classified as being ostium secundum, sinus venosus or ostium primum if it was located in the middle of atrial septum, superiorly in the region of the entrance of the superior vena cava into the right atrium, or in the basal portion of the atrial septum near the attachment of the atrioventricular valves, respectively (Figure 1).[5]

Size of atrial septal defect: The ASD size was determined by noting the maximum width of color flow signals across the defect taking into account various 2-dimensional echocardiographic planes (Figure 1).

Ratio of pulmonary to systemic blood flow: The ratio of pulmonary to systemic blood flow was calculated using the standard Doppler equation to calculate flow separately across the left and right ventricular outflow tracts, respectively: flow volume across left or right ventricular outflow tract (ml/min) = area of left or right ventricular outflow tract (cm^2) × mean velocity of flow across it (cm/second) × flow duration (seconds) × heart rate (beats/min). Left and right ventricular outflow tract areas were estimated by determining the maximum inner width immediately below the level of aortic and pulmonary valves in the parasternal long- and short-axis views, respectively, and by assuming both to be circular. These data were available in 26 of 45 patients who underwent cardiac catheterization. Mean velocities and flow durations in 20 of 26 patients were determined from pulsed Doppler spectral traces. These traces were generated by placing the pulsed Doppler sample volume in the flow area with the highest velocities as shown by the brightest color intensity levels displayed with color flow mapping both in the left and right ventricular outflow tracts (immediately below the semilunar valves), and imaged using the apical 5-chamber and parasternal short-axis views, respectively. A previously validated method analyzing the pixel color intensities was used to determine the mean velocities from color M-mode results in the remaining 6 patients because pulsed Doppler-derived velocities of left or right ventricular outflow tracts, or both, were not available to perform this analysis.[13,14] Pulmonary to systemic blood flow ratio could not be calculated in the remaining 19 patients as neither pulsed Doppler nor color M-mode examinations of left or right ventricular outflow tract, or both, were performed.

Shunt flow volume across atrial septal defect (Figure 2): The shunt flow volume across the ASD was quantitated in 24 of 45 patients who underwent cardiac catheterization using the standard Doppler method for calculating volume flow. ASD was assumed to be circular in configuration and the maximum width of the color flow signals moving across the defect was considered to represent the diameter of ASD: net shunt flow volume across ASD (ml/min) = area of ASD (cm^2) × mean flow velocity (cm/second) × total flow duration (seconds) × heart rate (beats/min). Shunt volume in ml/min was converted to liters/min by dividing it by 1,000.

Since this echocardiographic method only evaluates the shunt through ASD, it will not take into consideration additional shunting into the right atrium through another site. Thus, the echocardiographic data from patients with partial anomalous pulmonary veins were ex-

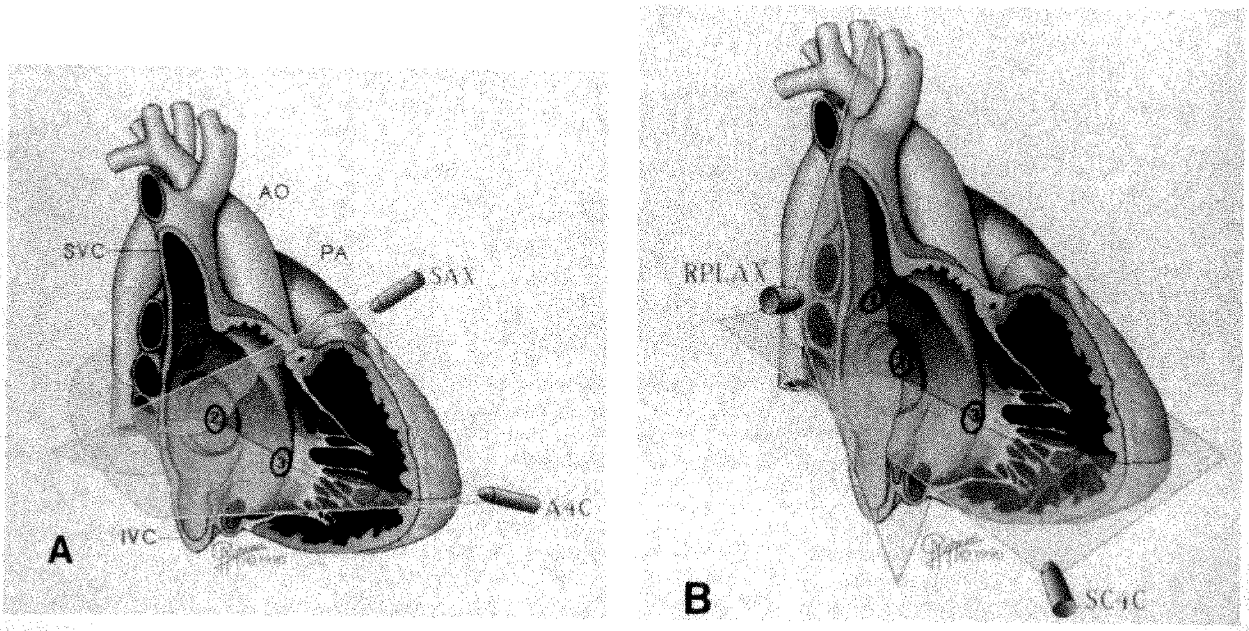

FIGURE 1. *A* **and** *B*, **transthoracic echocardiography in atrial septal defect. Various transthoracic echocardiographic planes used to image an atrial septal defect are shown passing through the heart depicted in the right anterior oblique view. 1 = sinus venosus defect; 2 = ostium secundum defect; 3 = ostium primum defect; AO = aorta; A4C = apical 4-chamber plane; IVC = inferior vena cava; PA = pulmonary artery; RPLAX = right parasternal long-axis plane; SAX = parasternal short-axis plane; SC4C = subcostal 4-chamber plane; SVC = superior vena cava.**

cluded from comparison with cardiac catheterization results, even though the shunt across the ASD could be calculated in them. In the remaining patients, shunt volume was not calculated because pulsed Doppler or color M-mode examination of the flow across the ASD was not performed. When the flow across the ASD was clearly identified using the right parasternal or subcostal imaging plane, the pulsed Doppler or the M-mode cursor was placed parallel to the shunt flow. Color Doppler was used to help guide the placement of the pulsed Doppler sample volume or the color M-mode cursor in the area of the brightest or aliased color flow signals to obtain the maximum velocity of the flow across the ASD. Recording speeds of 50 to 100 mm/s were used. The mean velocity of the flow across the ASD, over 1 cardiac cycle, was measured either on line or off line with a Nova Micro Systems, Inc. cardiac analysis system. For velocity measurements, pulsed Doppler was used in 17 and color M-mode[13,14] in the remaining 7 patients in whom pulsed Doppler interrogation of ASD flow was not performed. Minimal right to left shunt was not taken into consideration for calculation of shunt volume. A second independent observer performed all the measurements necessary for the calculation of shunt volume by 2-dimensional echocardiography and color Doppler.

Peak pulmonary artery systolic pressures: Tricuspid regurgitation, in the absence of pulmonary valve stenosis, was found by color Doppler to be present in 26 of 45 patients who underwent cardiac catheterization. Continuous-wave Doppler examinations were performed in these patients, but in only 18 of 26 patients, satisfactory traces were generated allowing peak systolic pulmonary arterial pressures to be calculated. These examinations were performed by placing the continuous-wave Doppler cursor parallel to the color flow signals representing tricuspid regurgitation and minimally adjusting the transducer to obtain peak velocities.[15] The peak pressure gradient across the tricuspid valve was calculated using the simplified Bernoulli equation. The peak pulmonary artery systolic pressure was obtained by adding an assumed right atrial pressure of 10 mm Hg to the pressure gradient calculated using the simplified Bernoulli equation.[15,16]

All the echocardiographic findings were correlated with equivalent surgical and catheterization and angiographic data using standard statistical methods.

Cardiac catheterization: In all 45 patients who underwent cardiac catheterization, pressure and oximetry measurements were obtained at various sites in the left and right heart. The pulmonary artery systolic pressure was <50 mm Hg in 39 of 45 patients and was 65, 70, 75, 75, 88 and 95 mm Hg, respectively, in the remaining 6 patients. In 28 of 45 patients, <15 days elapsed between the performance of cardiac catheterization and the color Doppler examination, and in 10 of 45 patients, between 15 days and 3 months elapsed between these examinations. For the remaining 7 patients, >3 months

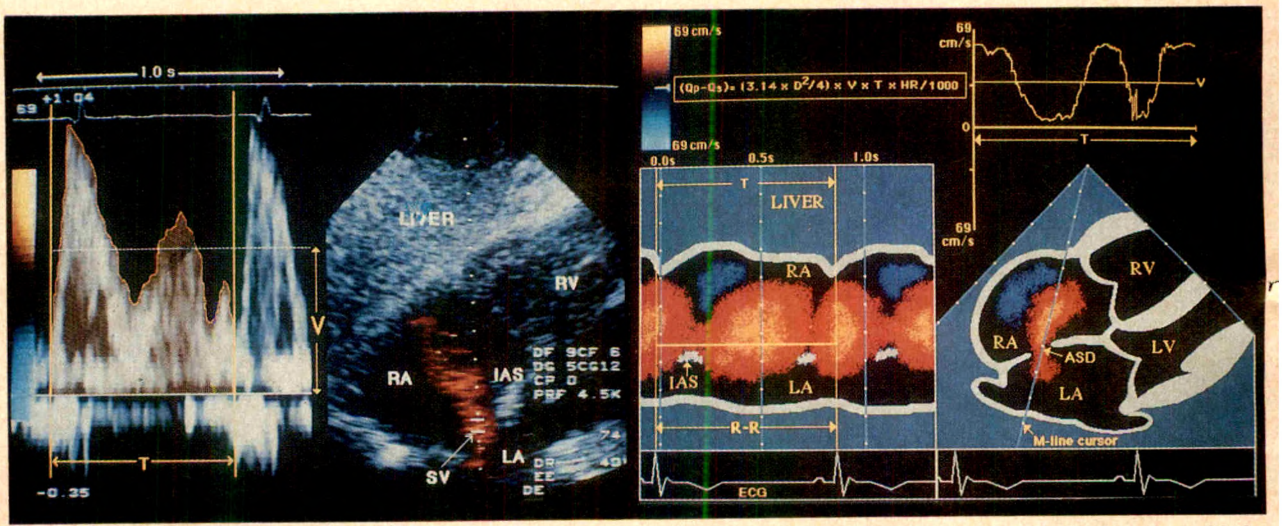

FIGURE 2. ***Left,*** **estimation of shunt flow volume across an atrial septal defect (ASD) by 2-dimensional and color Doppler-guided pulsed Doppler echocardiography. The area of the defect was calculated by assuming its shape to be circular and taking the maximum color Doppler jet width at the defect site as the diameter (cm). The shunt flow volume (Qp-Qs, liters/minute, 1/m) across the ASD was calculated as the product of the area of ASD (cm^2), mean flow velocity across the ASD (V cm/seconds, s), duration of blood flow across the ASD (T seconds, s) and the heart rate (HR) and dividing this by 1,000. The maximum color Doppler jet width at the site of the defect in the patient shown here was found to be 1.7 cm. Therefore, the area of the defect was estimated as $3.14 \times (1.7/2)^2$. The pulsed Doppler sample volume (SV) was placed at the defect site in the area of the brightest color signals and parallel to the flow direction to obtain a mean velocity (V) of 48 cm/s. The flow duration (T) was 0.71 second and the heart rate 78 beats/min. The Qp-Qs was calculated as the product of the area of the defect, mean velocity, duration of flow, heart rate and dividing this by 1,000: $3.14 \times (1.7/2)^2 \times 48 \times 0.71 \times 78/1{,}000 = 6.03$ liters/min.** ***Right,*** **estimation of shunt flow volume across an atrial septal defect (ASD) using color M-mode. In this case, the mean flow velocity across the ASD (V cm/second, s) was calculated by a computer using the color Doppler calibration bar and color intensity of the flow signals moving across the ASD. On the color Doppler calibration bar, the maximum color intensity (either red or blue), corresponds to the Nyquist limit and the velocity of M-mode color flow signals can thus be obtained by comparing their color intensity with respect to the color bar. The ASD shunt flow volume (Qp-Qs liters/minute, l/m) was then calculated as in the** ***left*** **figure. ECG = electrocardiogram; IAS = interatrial septum; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.**

had elapsed between these examinations. No evidence was found to indicate that a change in the clinical status of the patient had occurred during the period between the 2 examinations. Pulmonary to systemic flow ratios and shunt volumes were calculated in 40 patients using oximetry and the Fick principle. It was not calculated in the remaining 5 patients because oximetry was not performed. Angiography was performed in all patients by injection of a contrast agent into the main pulmonary artery and/or the right upper pulmonary vein in the anteroposterior, lateral and left anterior oblique views to determine the type of ASD and pulmonary venous connections.[17] Thirty-seven of these 45 patients underwent surgery.

Surgery: The surgeon noted the location and thus the type of ASD in each of the 42 patients who underwent surgery. In 24 of 42 patients, the surgeon also estimated the maximum size of ASD.

RESULTS

Diagnosis and location of atrial septal defect: Two-dimensional and color Doppler echocardiography correctly diagnosed the presence of ASD in 40 of 42 patients (95%) who underwent surgery. It correctly diagnosed all 31 patients with ostium secundum and all 6 patients with ostium primum ASD. It correctly diagnosed 2 of 5 patients with sinus venosus ASD, misdiagnosed 1 as having ostium secundum ASD and another 2 as having no ASD. The sensitivity and specificity of 2-dimensional and color Doppler echocardiography in the diagnosis of ostium secundum, ostium primum and sinus venosus ASD were 100 and 91%, 100 and 100%, and 40 and 100%, respectively. Two patients with a secundum ASD did not show a defect in the atrial septum using 2-dimensional echocardiography, but color flow signals were displayed moving from the left atrium into the right atrium through an apparently intact septum during the color Doppler examination. Both of these patients had previous surgery for ASD repair, but they were found during the current surgery to have a relatively small ASD resulting from a leak around the surgical patch. In 2 other patients, also with secundum ASD, a consistent defect was observed in the atrial septum by 2-dimensional echocardiography, but no color flow signals were observed moving through it using color Doppler. Both these patients had severe pulmonary valve stenosis with right ventricular systolic pressures of 85 and 109 mm Hg. Two-dimensional and color Doppler echocardiography failed to diagnose partial anomalous pulmonary venous connections noted at surgery in 3 of 5 patients with sinus venosus ASD.

Cardiac catheterization-angiocardiography correctly diagnosed the presence of ASD in all 37 patients (100%) who underwent both catheterization and surgery. It correctly diagnosed 24 of 26 patients with ostium secundum ASD, misdiagnosed 2 as ostium primum and misdiagnosed 1 as sinus venosus ASD. It correctly diagnosed 5 of 6 patients with ostium primum ASD and misdiagnosed 1 as ostium secundum ASD. It correctly diagnosed 4 of 5 patients with sinus venosus ASD and misdiagnosed 1 as ostium secundum. The sensitivity and specificity of cardiac catheterization-angiocardiography in diagnosing ostium secundum, ostium primum and sinus venosus ASD were 96 and 81%, 83 and 96%, and 80 and 97%, respectively. Partial anomalous pulmonary venous drainage, noted at surgery in 3 of 5 patients with sinus venosus ASD, was correctly diagnosed by catheterization-angiocardiography.

Size of atrial septal defect (Figure 3): No correlation was found between the maximum size of ASD measured by color Doppler and surgical estimation of ASD size in the 24 patients ($r = 0.50$) in whom both measurements were available. No correlation was also found between the maximum ASD size by color Doppler and shunt volume ($r = 0.50$) or pulmonary to systemic blood flow ratio ($r = 0.52$) by cardiac catheterization.

Pulmonary to systemic blood flow ratio (Figure 4): No correlation ($r = 0.38$) was found between the pulmonary to systemic blood flow ratios calculated by echocardiography and cardiac catheterization.

Shunt flow volume across atrial septal defect (Figure 5): A correlation coefficient of 0.74 was found comparing the shunt volumes by echocardiography and cardiac catheterization.

No statistically significant interobserver variability was noted when the shunt volumes by echocardiography were independently calculated by the second observer

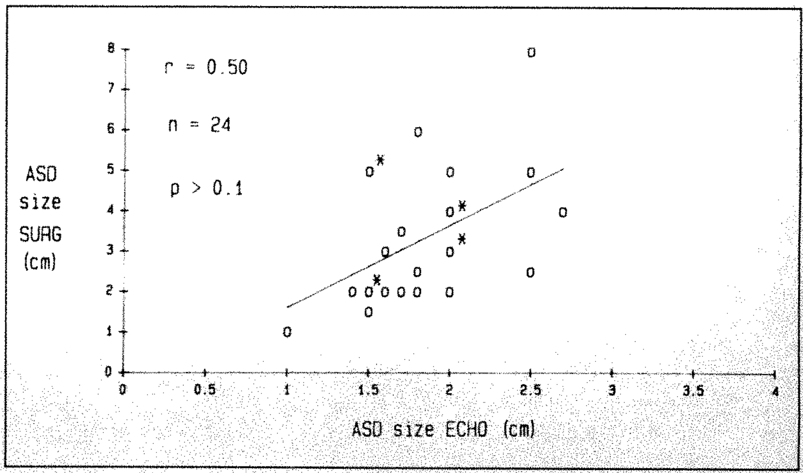

FIGURE 3. Atrial septal defect (ASD) size (centimeters, cm) by color Doppler echocardiography (ECHO) compared with surgical estimation (SURG). ***Asterisks*** **indicate overlapping values.**

(mean 7.64 ± 3.15 and 7.44 ± 2.76 liters, respectively, $p = 0.81$).

Peak pulmonary artery systolic pressure (Figure 6): The peak pulmonary artery systolic pressures obtained from color Doppler-guided continuous-wave Doppler correlated well with those obtained by cardiac catheterization ($r = 0.89$) in the 18 patients in whom adequate Doppler spectral traces were obtained.

DISCUSSION

In the present study, 2-dimensional and color Doppler echocardiography accurately detected an ASD in all except 2 surgically proven patients. It classified correctly all patients with ostium secundum and ostium primum ASD but misdiagnosed 3 of 5 patients with sinus venosus ASD. The technical difficulty in imaging the superior portion of the interatrial septum and the inferi-

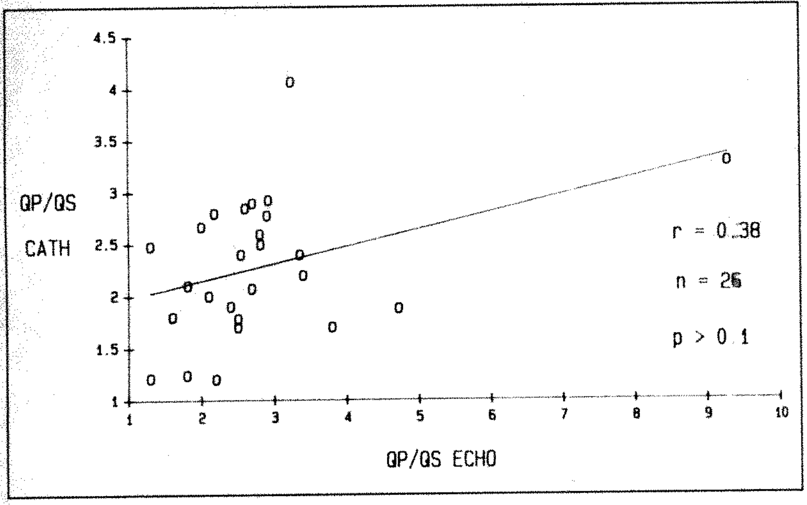

FIGURE 4. Pulmonary to systemic blood flow ratio (QP/QS) by echocardiography (ECHO) compared with cardiac catheterization (CATH).

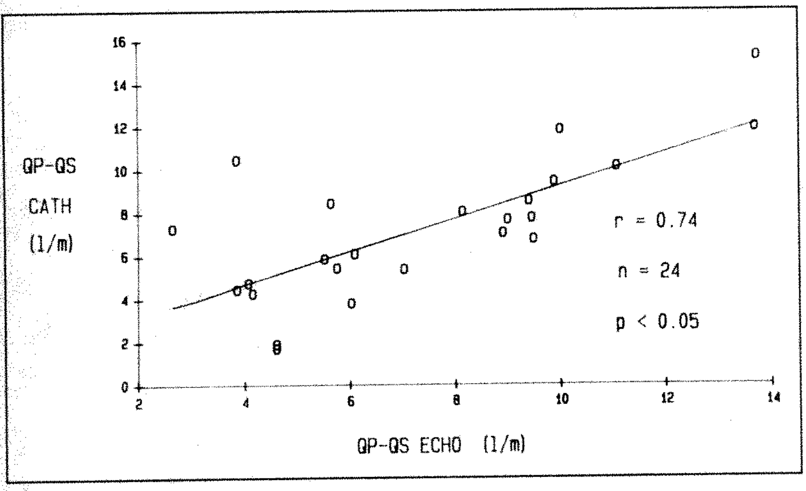

FIGURE 5. Shunt flow volume (liters/minute, l/m) across the atrial septal defect (QP-QS) by color Doppler echocardiography (ECHO) compared with cardiac catheterization (CATH).

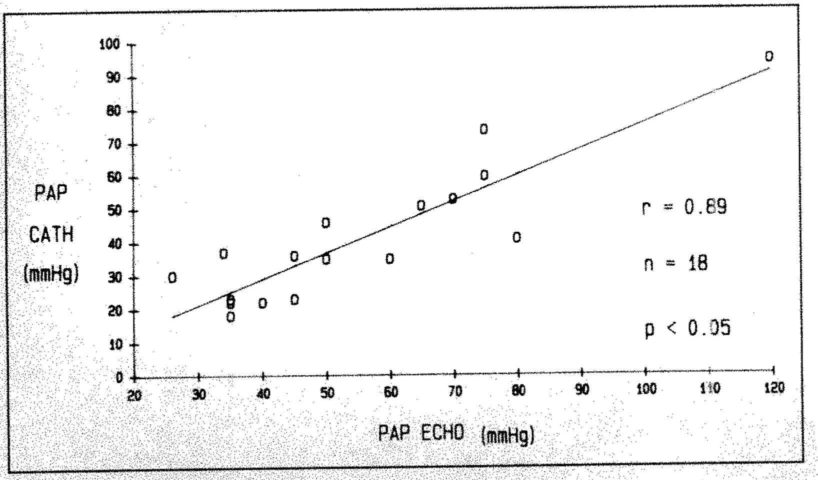

FIGURE 6. Peak pulmonary artery systolic pressures (PAP) obtained by color Doppler-guided conventional Doppler echocardiography (ECHO) compared with cardiac catheterization (CATH).

or portion of superior vena cava may explain the poor sensitivity of echocardiography in the detection of a sinus venosus ASD. It also could not identify the associated anomalous pulmonary veins present in 3 of 5 patients with sinus venosus ASD. On the other hand, cardiac catheterization and angiography detected all patients with ASD, but misclassified the type of ASD in 4 patients (2 ostium secundum, 1 ostium primum and 1 sinus venosus). All associated anomalous pulmonary veins were also correctly identified by cardiac catheterization and angiography. Thus, except for sinus venosus ASD and associated anomalous pulmonary venous connections, the accuracy of 2-dimensional and color Doppler echocardiography was comparable to that of cardiac catheterization and angiography in detecting and classifying ASD.

We also found color Doppler to be more accurate than 2-dimensional echocardiography in detecting relatively small leaks occurring around a previously repaired ASD. On the other hand, 2-dimensional echocardiography was found to be more accurate than color Doppler in the diagnosis of ASD associated with severe pulmonary valve stenosis. No color flow signals were observed moving through the ASD in these patients, although the ASD was consistently visualized by 2-dimensional echocardiographic imaging. The elevated right heart pressures would be expected to diminish both the volume and the velocity of the shunt flow which may have resulted in color Doppler not being able to display the flow through the ASD. Thus, 2-dimensional echocardiography and color Doppler were found to be complementary to each other in the diagnosis of relatively small ASDs and those complicated by severe right ventricular hypertension.

In the present study, the pulmonary to systemic blood flow ratio determined using echocardiography and cardiac catheterization showed a poor correlation ($r = 0.38$) even though the pulsed Doppler sample volume was guided by color Doppler. In previous studies, Stevenson et al[4] and Dittman et al[8] did not find good correlations between the Doppler and the cardiac catheterization estimation of this ratio when the shunts were large, especially when the ratios were >2:1. The mean flow ratio in our patients was also large (2.8:1). The poor correlation found by us may also have resulted from the several sources of errors that exist in determining this ratio by Doppler and 2-dimensional echocardiography.[18]

However, in our study, the shunt volume determined using 2-dimensional and color-guided conventional Doppler echocardiography correlated fairly well with the values determined from cardiac catheterization ($r = 0.74$). No calculations of the shunt volume have been attempted using pulsed Doppler interrogation of the color Doppler signals moving through the ASD. However, other color Doppler parameters, such as the ASD jet area in the right atrium, have been shown to correlate with shunt volume and shunt flow ratio both experimentally and in human subjects.[3,11] A significant limitation of these studies is the difficulty in differentiating the shunt signals in the right atrium from flow signals from superior and inferior vena cava, and those from tricuspid regurgitation which is often associated with ASD. Because of this difficulty, we decided to interrogate color Doppler flow signals only at the level of the defect where the chances of contamination from flow signals from other sources are minimal. Although in our patients, the shunt volume obtained by 2-dimensional and color Doppler echocardiography correlated fairly well with that obtained by cardiac catheterization, there are several limitations to this. A potential limitation of our method is the assumption that the cross-sectional area of an ASD is circular. Also, a small error in the measurement of the color Doppler jet width across the ASD could cause larger errors in the area measurements and, thus, significantly affect the values calculated for shunt volume. There are also significant limitations in calculating the pulmonary to systemic blood flow ratio and shunt volume by cardiac catheterization.[17,19-22]

In the present study, color Doppler-guided continuous-wave Doppler estimation of systolic pulmonary artery pressures correlated well with cardiac catheterization findings, and thus this noninvasive method may be of potential value in identifying patients with severe pulmonary hypertension that would be a contraindication for surgery.

In our patients, the size of the ASD measured during the color Doppler examination did not correlate well with the surgical estimate. The surgeons systematically estimated the defect to be larger than the echocardiographic measurement. During cardioplegia, the heart loses its tone and becomes flaccid and this may result in some overestimation of defect size at surgery. In contrast, in the presence of right ventricular hypertension, transdefect flow velocity may be so low that it may not be detected by color Doppler, resulting in underestimation of ASD size. Unlike the previous study by Pollick et al,[11] the maximum ASD jet width by color Doppler did not correlate well with pulmonary to systemic blood flow ratio or shunt volume by cardiac catheterization in our patients.

Acknowledgment: We deeply appreciate the contributions of Elizabeth F. Philpot in providing editorial assistance in the preparation of this manuscript and those of Adelino Parro Jr., MD, in helping with statistical analysis.

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Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks and Whites With Systemic Hypertension and With and Without Echocardiographic and Electrocardiographic Evidence of Left Ventricular Hypertrophy

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Hypertension was present in 50% of 196 blacks and in 36% of 382 whites ($p < 0.001$). A prospective study of 84 elderly blacks (70% women) and 326 elderly whites (73% women) with hypertension correlated echocardiographic and electrocardiographic left ventricular (LV) hypertrophy with incidences of congestive heart failure (CHF), coronary events and atherothrombotic brain infarction (ABI). Echocardiographic LV hypertrophy ($p < 0.02$) and concentric LV hypertrophy ($p < 0.001$) were more prevalent in hypertensive blacks than in hypertensive whites. Hypertensive blacks were younger (78 ± 9 years) than hypertensive whites (82 ± 7 years) ($p < 0.001$). Other coronary risk factors were similar, except for higher serum triglycerides in whites than in blacks ($p < 0.02$). Follow-up was 37 ± 18 months in blacks and 43 ± 18 months in whites ($p < 0.01$). Incidences of CHF and coronary events were not significantly different in blacks and whites. ABI incidence was 38% in blacks and 21% in whites ($p < 0.005$). Multiple logistic regression analysis showed that prior CHF ($p = 0.000$), concentric LV hypertrophy ($p = 0.018$) and echocardiographic LV hypertrophy ($p = 0.022$) were independent risk factors for CHF. Echocardiographic LV hypertrophy ($p = 0.001$), serum total cholesterol ($p = 0.002$), concentric LV hypertrophy ($p = 0.005$) and prior coronary artery disease ($p = 0.042$) were independent risk factors for coronary events. Prior ABI ($p = 0.001$), echocardiographic LV hypertrophy ($p = 0.001$) and electrocardiographic LV hypertrophy ($p = 0.034$) were independent risk factors for ABI.

(Am J Cardiol 1991;67:295–299)

Systemic hypertension is an independent risk factor for congestive heart failure (CHF), coronary artery disease and atherothrombotic brain infarction (ABI). Hypertension is more prevalent among black than among white Americans.[1,2] Black Americans have the highest risk for hypertension-related morbidity and mortality.[2-4] Black hypertensives have a higher prevalence of left ventricular (LV) hypertrophy and a higher incidence of stroke and CHF than white hypertensives.[2] Mortality from stroke causes a larger percentage of deaths from cardiovascular disease among blacks than among whites.[3,4] Black hypertensives in the Hypertension Detection Follow-Up Program had a higher prevalence of electrocardiographic LV hypertrophy, a higher incidence of stroke, and a higher mortality rate for all causes than white hypertensives.[5,6]

Patients with electrocardiographic[7-9] or echocardiographic[9-15] LV hypertrophy have an increased incidence of cardiovascular morbidity and mortality. At similar blood pressure levels, the prevalence of echocardiographic LV hypertrophy diagnosed by increased LV mass was 2 times greater and the prevalence diagnosed by increased relative wall thickness was 3 times greater in hypertensive blacks than in hypertensive whites.[16] We report data from a prospective study correlating electrocardiographic and echocardiographic LV hypertrophy with the incidences or frequencies of CHF, new coronary events, and new ABI in elderly blacks and whites with systemic hypertension.

METHODS

Of 1,322 patients >62 years of age in a long-term health care facility, 1,072 (81%) were white, 196 (15%) were black, 50 (4%) were Hispanic and 4 (<1%) were Asian. A systolic blood pressure of ≥160 mm Hg on 3 occasions was considered systolic hypertension.[2] A diastolic blood pressure of ≥90 mm Hg on 3 occasions was considered diastolic hypertension.[2] Patients with hypertension had systolic or diastolic hypertension at the onset of the study or were receiving antihypertensive therapy at the onset of the study for documented hypertension. Of 499 patients with hypertension, 289 (58%) were on antihypertensive medication before the study. Isolated systolic hypertension was present in 256 of 499 patients (51%) with hypertension. All patients with hyper-

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TABLE I Prevalence of Hypertension and Associated Echocardiographic and Electrocardiographic Left Ventricular (LV) Hypertrophy in Elderly Blacks and Whites

	Blacks		Whites		
	No.	(%)	No.	(%)	p Value
Hypertension	98/196	(50)	382/1,072	(36)	<0.001
Echocardiographic LV hypertrophy in patients with hypertension	60/84	(71)	183/326	(56)	<0.02
Electrocardiographic LV hypertrophy in patients with hypertension	17/84	(20)	48/326	(15)	NS
Concentric LV hypertrophy in patients with hypertension	50/84	(60)	129/326	(40)	<0.001
Eccentric LV hypertrophy in patients with hypertension	10/84	(12)	54/326	(17)	NS

NS = not significant.

TABLE II Prevalence of Coronary Risk Factors in Elderly Blacks and Whites with Hypertension

	Blacks (n = 84)	Whites (n = 36)	p Value
Male sex	25 (30%)	87 (27%)	NS
Female sex	59 (70%)	239 (73%)	NS
Age (yr)	78 ± 9	82 ± 7	<0.001
Follow-up (mos)	37 ± 18	43 ± 18	<0.01
Cigarette smoking	6 (7%)	26 (8%)	NS
Diabetes mellitus	25 (30%)	90 (28%)	NS
Obesity	11 (13%)	27 (8%)	NS
Serum total cholesterol (mg/dl)	217 ± 56	215 ± 47	NS
Serum HDL cholesterol (mg/dl)	47 ± 15	46 ± 14	NS
Serum total cholesterol/HDL cholesterol	5.1 ± 2.0	5.1 ± 1.8	NS
Serum triglycerides (mg/dl)	121 ± 65	143 ± 84	<0.02
Prior CHF	12 (14%)	47 (14%)	NS
Prior coronary artery disease	45 (54%)	163 (50%)	NS
Prior ABI	47 (56%)	101 (31%)	<0.001

ABI = atherothrombotic brain infarction; CHF = congestive heart failure; HDL = high-density lipoprotein; NS = not significant.

tension were treated during the study. No patients were excluded for reasons other than age.

M-mode and 2-dimensional echocardiograms and electrocardiograms were obtained as previously described,[9,12] prospectively at study entry in the 98 blacks, 382 whites, 17 Hispanics and 2 Asians with hypertension. Technically adequate M-mode or 2-dimensional echocardiograms for measuring LV transverse dimension, posterior wall thickness, and interventricular septal thickness at end diastole, using the Penn convention[17] to determine LV mass and American Society for Echocardiography criteria[18] to calculate relative wall thickness,[19] were obtained in 84 of 98 blacks (86%), 326 of 382 whites (85%), 14 of 17 Hispanics (82%) and 2 of 2 Asians (100%).

Measurements were obtained from the 2-dimensional study in 54% of patients. The formula[17,20] to determine LV mass was LV mass (g) = 1.04 [(LV diastolic dimension + posterior wall thickness + interventricular septal thickness during diastole)^3 − (LV diastolic dimension)^3] − 13.6. LV hypertrophy was diagnosed if the LV mass exceeded 110 g/m^2 in women and 134 g/m^2 in men.[20] The formula[19] to determine relative wall thickness was relative wall thickness = 2 × posterior wall thickness/LV internal diastolic dimension. Concentric LV hypertrophy was diagnosed if the patient had increased LV mass index plus a relative wall thickness $\geq$0.45.[19] Eccentric LV hypertrophy was diagnosed if the patient had increased LV mass index and a relative wall thickness <0.45.[19]

Electrocardiograms were interpreted by a cardiologist (WSA) before interpretation of the echocardiograms. Electrocardiographic LV hypertrophy was diagnosed if the point score of Romhilt and Estes was $\geq$5.[21]

Other coronary risk factors evaluated were current cigarette smoking, diabetes mellitus, obesity, serum total cholesterol, serum high-density lipoprotein cholesterol and serum triglycerides. All blood pressure and risk factor data were obtained prospectively. Diabetes mellitus was diagnosed if the patient was receiving insulin or oral hypoglycemic drugs to control hyperglycemia or if the fasting venous plasma glucose levels were $\geq$140 mg/dl on 2 occasions. The weight and height of each patient were correlated with the average height-weight table for persons aged 65 to 94 years.[22] The patient was considered obese if he or she was $\geq$20% above ideal body weight. Blood was drawn after a 14-hour overnight fast for determination of serum total cholesterol, high-density lipoprotein cholesterol and triglycerides by Smith Kline Clinical Laboratories, Inc.

CHF was diagnosed if 2 criteria were satisfied: (1) pulmonary basilar rales were heard by 2 physicians, including a cardiologist, and (2) pulmonary vascular congestion was present on the chest x-rays interpreted by both an experienced radiologist and cardiologist. New coronary events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation, or sudden cardiac death. Myocardial infarction was documented as previously described.[23] Sudden cardiac death was defined as an unexpected cardiac death in a patient found dead within 1 hour of being clinically stable.[24] New ABI was diagnosed by a neurologist as previously described.[12]

For analyses comparing 2 groups, chi-square tests were used for dichotomous variables, and Student's *t* tests were applied to continuous variables. Comparison between subjects who developed new coronary events and those who did not was made using multiple logistic regression to determine which combination of prognostic variables was most suitable for predicting coronary events. Multiple logistic regressions were also performed for CHF and ABI. The independent variables incorporated in the multiple logistic regression are race (black and white), sex, age, echocardiographic LV hypertrophy, concentric LV hypertrophy, electrocardiographic LV hypertrophy, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, cigarette smoking, diabetes mellitus, obesity, and prior

TABLE III Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks and Whites with Hypertension

	Blacks (n = 84)		Whites (n = 326)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	32	(38)	118	(36)	0.747
Coronary events	47	(56)	160	(49)	0.261
Atherothrombotic brain infarction	32	(38)	68	(21)	<0.005

TABLE IV Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks With Hypertension and With and Without Echocardiographic Left Ventricular (LV) Hypertrophy

	LV Hypertrophy (n = 60)		No LV Hypertrophy (n = 24)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	29	(48)	3	(13)	<0.005
Coronary events	42	(70)	5	(21)	<0.001
Atherothrombotic brain infarction	28	(47)	4	(17)	<0.02

TABLE V Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Whites With Hypertension and With and Without Echocardiographic Left Ventricular (LV) Hypertrophy

	LV Hypertrophy (n = 183)		No LV Hypertrophy (n = 143)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	96	(52)	22	(15)	<0.001
Coronary events	124	(68)	36	(25)	<0.001
Atherothrombotic brain infarction	55	(30)	13	(9)	<0.001

CHF, coronary artery disease and ABI. Follow-up was 6 to 64 months. No patients were lost to follow-up.

RESULTS

Because of the small number of Hispanics and Asians studied, data from these 2 groups are not presented. Table I lists the prevalence of hypertension in elderly blacks and whites and the prevalence of echocardiographic LV hypertrophy, electrocardiographic LV hypertrophy, concentric LV hypertrophy and eccentric LV hypertrophy in blacks and whites with hypertension. Table II lists the prevalence of male sex, female sex, cigarette smoking, diabetes mellitus, obesity, and prior CHF, coronary artery disease and ABI, as well as the mean age, follow-up, serum total cholesterol, serum high-density lipoprotein cholesterol, serum total cholesterol/high-density lipoprotein cholesterol and serum triglycerides in elderly blacks and whites with hypertension.

Table III lists the incidences of CHF, coronary events and ABI in blacks and whites with hypertension.

TABLE VI Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks With Hypertension and With and Without Electrocardiographic Left Ventricular (LV) Hypertrophy

	LV Hypertrophy (n = 17)		No LV Hypertrophy (n = 67)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	8	(47)	24	(36)	0.394
Coronary events	13	(76)	34	(51)	0.056
Atherothrombotic brain infarction	10	(59)	22	(33)	<0.05

TABLE VII Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Whites With Hypertension and With and Without Electrocardiographic Left Ventricular (LV) Hypertrophy

	LV Hypertrophy (n = 48)		No LV Hypertrophy (n = 278)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	25	(52)	93	(33)	<0.05
Coronary events	31	(65)	129	(46)	<0.02
Atherothrombotic brain infarction	17	(35)	51	(18)	<0.01

TABLE VIII Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Blacks with Hypertension and Concentric and Eccentric Left Ventricular (LV) Hypertrophy

	Concentric LV Hypertrophy (n = 50)		Eccentric LV Hypertrophy (n = 10)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	26	(52)	3	(30)	0.204
Coronary events	37	(74)	5	(50)	0.131
Atherothrombotic brain infarction	24	(48)	4	(40)	0.643

Table IV lists the incidences of CHF, coronary events and ABI in blacks with hypertension and with and without echocardiographic LV hypertrophy. Table V lists the incidences of CHF, coronary events and ABI in whites with hypertension and with and without echocardiographic LV hypertrophy. Table VI lists the incidences of CHF, coronary events and ABI in blacks with hypertension and with and without electrocardiographic LV hypertrophy. Table VII lists the incidences of CHF, coronary events and ABI in whites with hypertension and with and without electrocardiographic LV hypertrophy. Table VIII lists the incidences of CHF, coronary events and ABI in blacks with hypertension and concentric and eccentric LV hypertrophy. Table IX lists the incidences of CHF, coronary events and ABI in whites with hypertension and concentric and eccentric LV hypertrophy.

Tables X, XI and XII list the results of fitting multiple logistic regression models for CHF (Table X), coro-

TABLE IX Incidences of Congestive Heart Failure, Coronary Events and Atherothrombotic Brain Infarction in Elderly Whites with Hypertension and Concentric and Eccentric Left Ventricular (LV) Hypertrophy

	Concentric LV Hypertrophy (n = 129)		Eccentric LV Hypertrophy (n = 54)		
	No.	(%)	No.	(%)	p Value
Congestive heart failure	78	(60)	18	(33)	<0.001
Coronary events	96	(74)	28	(52)	<0.005
Atherothrombotic brain infarction	39	(30)	16	(30)	0.935

TABLE X Prognostic Variables for Congestive Heart Failure and Their Regression Coefficients in the Final Multiple Logistic Regression Model

Variable	Regression Coefficient	Standard Error	p Value	Odds Ratio
Prior congestive heart failure	3.7211	0.6210	0.000	41.31
Concentric LV hypertrophy	0.8916	0.3616	0.018	2.44
Echocardiographic LV hypertrophy	0.9449	0.3973	0.022	2.57
Serum total cholesterol	0.0043	0.0032	0.185	1.00
Serum high-density lipoprotein cholesterol	−0.0144	0.0108	0.199	0.99
Serum triglycerides	−0.0026	0.0021	0.229	1.00
Prior atherothrombotic brain infarction	0.3397	0.2735	0.230	1.40
Cigarette smoking	−0.5630	0.4906	0.267	0.57
Race	0.3792	0.3314	0.269	1.46
Prior coronary artery disease	0.2343	0.2589	0.382	1.26
Sex	−0.1678	0.2884	0.574	0.85
Age	0.0016	0.0184	0.933	1.00
Electrocardiographic LV hypertrophy	−0.0277	0.3447	0.938	0.97
Diabetes mellitus	0.0013	0.3010	0.966	1.00
Obesity	0.0015	0.4691	1.000	1.00
Constant	−2.4884	1.7110	0.160	0.08

Race = 0 if black and 1 if white; sex = 0 if male and 1 if female.
LV = left ventricular.

nary events (Table XI) and ABI (Table XII). Odds ratios, 95% confidence limits, for echocardiographic LV hypertrophy are 2.57 (1.18 to 5.60) for CHF, 3.21·(1.67 to 6.15) for coronary events and 4.17 (1.91 to 9.13) for ABI.

DISCUSSION

Coronary artery disease prevalence and mortality rates are similar in black and white men and higher in black women than in white women.[25] Long-term survival of blacks with angiographically documented coronary artery disease is lower in blacks than in whites.[26] LV hypertrophy and decreased diastolic function associated with hypertension contribute to this excess mortality.[26] LV hypertrophy is probably the most important factor accounting for the poor prognosis of blacks after myocardial infarction.[27]

TABLE XI Prognostic Variables for Coronary Events and Their Regression Coefficients in the Final Multiple Logistic Regression Model

Variable	Regression Coefficient	Standard Error	p Value	Odds Ratio
Echocardiographic LV hypertrophy	1.1655	0.3323	0.001	3.21
Serum total cholesterol	0.0099	0.0030	0.002	1.01
Concentric LV hypertrophy	0.9685	0.3327	0.005	2.63
Prior coronary artery disease	0.5007	0.2371	0.042	1.65
Age	0.0275	0.0170	0.118	1.03
Cigarette smoking	0.7087	0.4623	0.138	2.03
Prior congestive heart failure	0.5361	0.3597	0.150	1.71
Sex	−0.3984	0.2674	0.150	0.67
Diabetes mellitus	0.3945	0.2771	0.169	1.48
Serum high-density lipoprotein cholesterol	−0.0128	0.0092	0.179	0.99
Prior atherothrombotic brain infarction	−0.3325	0.2579	0.213	0.72
Obesity	0.4067	0.4202	0.349	1.50
Serum triglycerides	−0.0016	0.0019	0.416	1.00
Electrocardiographic LV hypertrophy	0.1044	0.3335	0.762	1.11
Race	−0.0602	0.3114	0.852	0.94
Constant	−4.7162	1.5760	0.004	0.01

Race = 0 if black and 1 if white; sex = 0 if male and 1 if female.
LV = left ventricular.

TABLE XII Prognostic Variables for Atherothrombotic Brain Infarction and Their Regression Coefficients in the Final Multiple Logistic Regression Model

Variable	Regression Coefficient	Standard Error	p Value	Odds Ratio
Prior atherothrombotic brain infarction	0.9560	0.2670	0.001	2.60
Echocardiographic LV hypertrophy	1.4290	0.3990	0.001	4.17
Electrocardiographic LV hypertrophy	0.7432	0.3250	0.034	2.10
Prior coronary artery disease	−0.4869	0.2620	0.085	0.61
Age	−0.0311	0.0180	0.106	0.97
Race	−0.3949	0.3070	0.233	0.67
Diabetes mellitus	0.2771	0.2920	0.378	1.32
Serum total cholesterol	−0.0030	0.0032	0.383	1.00
Cigarette smoking	−0.4260	0.4750	0.405	0.65
Sex	−0.2480	0.2880	0.424	0.78
Serum high-density lipoprotein cholesterol	0.0083	0.0110	0.465	1.01
Prior congestive heart failure	−0.2121	0.3690	0.594	0.81
Serum triglycerides	0.0011	0.0020	0.625	1.00
Obesity	−0.1494	0.4380	0.751	0.86
Concentric LV hypertrophy	0.0490	0.3490	0.895	1.05
Constant	0.6341	1.6400	0.720	1.89

Race = 0 if black and 1 if white; sex = 0 if male and 1 if female.
LV = left ventricular.

Hypertension is the most significant cause of stroke in blacks and in whites. Black men are 2.5 times as likely to die of stroke than white men.[28] Black women are 2.4 times as likely to die of stroke than white women.[28]

Casale et al[10] demonstrated at 4.8-year follow-up of men with uncomplicated hypertension that echocardiographic LV hypertrophy was the most important independent risk factor for future cardiovascular events. Levy et al[11] showed at 4-year follow-up that echocardiographic LV hypertrophy was an independent risk factor for new coronary events in elderly men and women in the Framingham study. Levy et al[15] also showed at 4-year follow-up in men and in women ≥40 years of age in the Framingham study that echocardiographic LV hypertrophy was an independent risk factor for incidence of cardiovascular disease, mortality from cardiovascular disease and mortality from all causes. Cooper et al[14] demonstrated in a predominantly black population with coronary artery disease and a high prevalence of hypertension and LV hypertrophy that echocardiographic LV hypertrophy was a prognostic factor independent of LV ejection fraction and obstructive coronary artery disease. Echocardiographic measures of LV hypertrophy were the most important predictors of survival.[14]

Our study of elderly patients showed a higher prevalence of hypertension in blacks than in whites and a higher prevalence of echocardiographic LV hypertrophy and concentric LV hypertrophy in hypertensive blacks than in hypertensive whites. Our hypertensive blacks were younger than our hypertensive whites. Other coronary risk factors were similar, except for higher mean serum triglycerides in whites. Follow-up was shorter in blacks (37 months) than in whites (43 months). All patients with hypertension were treated with antihypertensive drugs. The incidences of CHF and coronary events were not significantly different in blacks and whites. However, the prevalence of prior ABI and the incidence of new ABI were higher in blacks than in whites.

Multiple logistic regression analysis showed that prior CHF (most important), concentric LV hypertrophy (second most important) and echocardiographic LV hypertrophy (third most important) were independent risk factors for CHF in our hypertensive elderly population. Echocardiographic LV hypertrophy (most important), serum total cholesterol (second most important), concentric LV hypertrophy (third most important) and prior coronary artery disease (fourth most important) were independent risk factors for new coronary events in our hypertensive elderly population. Prior ABI (most important), echocardiographic LV hypertrophy (second most important) and electrocardiographic LV hypertrophy (third most important) were independent risk factors for ABI in our hypertensive elderly population.

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Evaluation of the Pharmacokinetics and Electrocardiographic Effects of Intravenous Verapamil with Intravenous Calcium Chloride Pretreatment in Normal Subjects

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To evaluate the effects of calcium pretreatment on the disposition and electrocardiographic effects of verapamil, 8 healthy male volunteers received treatment in each of 3 phases in a randomized, double-blind, crossover manner. Phase I denoted 10 ml of 0.9% intravenous sodium chloride followed by 10 mg of intravenous verapamil; phase II denoted 10 ml of 10% intravenous calcium chloride followed by 4 ml of 0.9% intravenous sodium chloride; and phase III denoted 10 ml of 10% intravenous calcium chloride followed by 10 mg of intravenous verapamil. Blood samples for the determination of verapamil concentrations were drawn at 5, 10, 15, 20, 30, 45, 60 and 90 minutes, and at 2, 4, 6, 10 and 24 hours. Blood pressure, heart rate and PR intervals were also measured at these times. Pretreatment of verapamil with intravenous calcium did not alter the disposition of intravenous verapamil. Blood pressure was not significantly altered in any treatment phase, although calcium tended to increase mean arterial pressure and verapamil abolished this effect. Calcium had no significant affect on verapamil-induced PR prolongation (maximum percent change in PR interval: phase I = 19 ± 11%, phase III = 18 ± 7%; time to maximal prolongation: phase I = 0.38 ± 0.21 hours, phase III = 0.37 ± 0.26 hours; and area under the percent change in PR vs time curve: phase I = 15.5 ± 10, phase III = 21 ± 9). Verapamil caused a reflex increase in heart rate of similar magnitude in both phases I and III (24 ± 10% and 21 ± 7%, respectively). However, calcium in phase III caused an initial decrease in heart rate, such that the net change in heart rate over time was significantly different (p <0.05) than with verapamil alone (area under the percent change in heart rate vs time curve: phase I = 5 ± 28, phase III = −23 ± 12). In doses frequently used in a clinical setting, calcium and verapamil produce opposing effects on the sinus rate and arterial blood pressure, but not on atrioventricular conduction. These findings show that the atrioventricular nodal and thus antiarrhythmic effects of verapamil are preserved despite pretreatment with calcium.

(Am J Cardiol 1991;67:300–304)

Intravenous verapamil is very effective in the treatment of supraventricular tachyarrhythmias[1-4]; however, its usefulness may occasionally be limited by hypotension.[5,6] The beneficial potential of intravenous calcium salts to reverse verapamil-induced hypotension was first reported anecdotally in association with a verapamil overdose.[7] Since then, several investigators reported that intravenous calcium may lessen the hypotensive effect of intravenous verapamil without altering its antiarrhythmic effect.[5,6,8-11] However, neither the potential pharmacokinetic interaction nor the pharmacodynamic aspects of this combination have been fully delineated. Therefore, we conducted a randomized, double-blind, crossover study in normal volunteers to characterize further the pharmacokinetic and electrocardiographic effects of intravenous verapamil with and without intravenous calcium chloride pretreatment.

METHODS

Subjects: Male volunteers aged 18 to 35 years were considered for participation. Screening procedures consisted of a medical history, physical examination, 12-lead electrocardiography, serum chemistries and complete blood count. Subjects were excluded from consideration if there was evidence of: (1) organic heart disease; (2) atrioventricular heart block, sinus bradycardia or tachycardia, or the presence of any other supraventricular or ventricular arrhythmias; (3) systolic blood pressure >150 mm Hg or <110 mm Hg, or diastolic blood pressure >95 mm Hg or <55 mm Hg; (4) any clinically significant laboratory abnormalities; (5) history of regular use of any medications, tobacco or illicit drugs; or (6) the presence of any other serious medical condition. A total of 9 subjects were enrolled in the study; however, 1 subject dropped out after the first phase for reasons unrelated to the protocol. Therefore, 8

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healthy, nonsmoking men (mean age ± standard deviation 26 ± 4 years, weight 75.6 ± 8.2 kg) completed all 3 phases of the study and are the subject of the present report. This study was approved by the university institutional review board for human investigations and all subjects provided oral and written informed consent.

Procedures: Subjects were asked to abstain from taking any medications, caffeine or alcohol for ≥48 hours before the start of each treatment phase until its completion. After an overnight fast, an intravenous catheter was placed in both arms of the subjects and flushed with a dilute heparin solution (10 U/ml). One catheter was used for drug administration, the other for blood sampling. The subjects received treatment in each of 3 phases in a randomized, double-blind, crossover manner. In phase I, subjects received 10 ml of 0.9% sodium chloride followed by 10 mg of verapamil (4 ml). In phase II, subjects received 10 ml of a 10% solution of calcium chloride (13.6 mEq) followed by 4 ml of 0.9% sodium chloride. In phase III, subjects received 10 ml of a 10% solution of calcium chloride followed by 10 mg of verapamil. Treatment phases were separated by a washout period ≥1 week. Calcium chloride or calcium-placebo was administered manually by intravenous push over 5 to 7 minutes, depending on subject tolerance. Verapamil or verapamil-placebo was administered 5 minutes after the completion of calcium or calcium-placebo injection via a volumetric intravenous syringe pump over 5 minutes. All solutions were followed by a saline flush.

Subjects maintained a supine position from ≥15 minutes before until 2 hours after drug administration. Before calcium chloride or calcium-placebo administration, a baseline blood sample, blood pressure measurements and a 1-minute (lead II) electrocardiographic rhythm strip (recorded at 50 mm/s) were obtained. Blood pressure measurements were obtained with an automated blood pressure device (HealthTeam model 8175, M.E. Team Inc., South Plainfield, New Jersey) to decrease the variability in measurement. Blood pressure was remeasured and rhythm strip obtained again before verapamil or verapamil-placebo administration. Thereafter, blood pressure measurements, rhythm strip and a 10-ml blood sample were obtained at 5, 10, 15, 20, 30, 45, 60, 75 and 90 minutes, and at 2, 4, 6, 10 and 24 hours after verapamil administration. Blood samples were allowed to clot at room temperature, then centrifuged and separated. The serum was stored at −70°C until analysis of the verapamil concentrations.

Racemic verapamil serum concentrations were measured by a reverse-phase, high-performance liquid chromatographic assay using fluorometric detection. Serum samples were spiked with the internal standard (metoprolol) and extracted by the liquid-liquid method of Harapat and Kates.[12] Separation and quantitation of verapamil was performed using the methodology of Kuwada et al,[13] with the substitution of octane-sulfonic acid for heptane-sulfonic acid in the mobile phase. The intra- and interday coefficients of variation were <11% for verapamil concentrations ranging from 6.5 to 65 ng/ml. The lower limit of quantitation for verapamil was 5 ng/ml.

Pharmacokinetic analysis: Racemic verapamil serum concentration versus time data was analyzed by weighted, nonlinear, least-squares regression using the RSTRIP (MicroMath Inc., Salt Lake City, Utah) and PCNONLIN (SCI Software, Statistical Consultants Inc., Lexington, Kentucky) computer programs. Single and multiple compartment models were fit to the data, which was weighted by a factor of 1/y. Model discrimination was performed by: (1) the Akaike information criteria,[14] (2) the F ratio test, (3) the examination of the residuals and comparative sums of squares, and (4) visual inspection for the line of best fit. The terminal rate constant was objectively determined from the terminal slope of the fitted concentration versus time curve. The area under the concentration versus time curve and area under the moment curve were calculated using the trapezoidal rule and extrapolated to infinity. The remaining pharmacokinetic parameters were calculated in a noncompartmental manner from the parameters above, using standard equations for a constant rate infusion of short duration.[15]

Hemodynamic and electrocardiographic analysis: Mean arterial blood pressure was calculated by diastolic pressure plus 1/3 pulse pressure. Heart rate and PR intervals were determined from the mean of 10 consecutive cardiac cycles on each electrocardiographic rhythm strip. Heart rate, PR interval, systolic, diastolic and mean arterial blood pressure (effect variables) were statistically evaluated over time within treatment phases to detect significant changes from baseline, as well as to determine the duration of pharmacologic effect. Percent changes from baseline were calculated for heart rate and PR interval to compare the maximal effect and time to maximal effect between treatment phases. Area under the percent change (effect) versus time curve was calculated from time 0 to 2 hours by the trapezoidal rule to compare the time-averaged net effects between treatment phases.

Statistical analysis: The pharmacokinetic parameters of the 2 verapamil phases were compared using Wilcoxon's matched pairs test. Differences within treatment phases were analyzed by a nonparametric equivalent of an analysis of variance for repeated measures. Differences among the 3 treatment phases were evaluated by a nonparametric equivalent of a 2-way analysis of variance. The Student-Newman-Keuls multiple comparison test was used to determine which groups differed according to the analysis of variance.[16] Statistical significance was defined as $p < 0.05$ for all comparisons. All data are reported as the mean ± standard deviation.

RESULTS

Pharmacokinetics: A 3-compartment model best fit the concentration-time data in all subjects, according to the Akaike information criteria and the F ratio test, which was confirmed by the examination of residuals and by visual inspection of fit. Table I lists the mean pharmacokinetic parameters for the 2 verapamil treatment phases (I and III). The pharmacokinetics of intravenous verapamil were not significantly altered by pretreatment with intravenous calcium chloride.

TABLE I Pharmacokinetic Parameters of Verapamil

Parameter	Phase I (Verapamil)	Phase III (Ca^{++}/Verapamil)	p Value
V_{SS} (liters/kg)	3.24 ± 0.62	3.23 ± 1.04	NS
CL (liters/hr)	66.8 ± 5.7	64.4 ± 8.2	NS
Half-life (hrs)	3.6 ± 0.9	3.7 ± 1.2	NS
k (hrs^{-1})	0.203 ± 0.047	0.204 ± 0.058	NS

Values are the mean ± standard deviation.
CL = systemic clearance; k = terminal rate constant; NS = difference not significant; V_{SS} = volume of distribution at steady state.

TABLE II Comparison of Drug-Induced Effects Using Baseline Values Before Verapamil

	Phase I (Verapamil)	Phase III (Ca^{++}/Verapamil)	p Value
Max % PR	19 ± 11	18 ± 7	NS
$Tmax_{PR}$	0.38 ± 0.21	0.37 ± 0.26	NS
Auc_{PR}	15.5 ± 10	21 ± 9	NS
Max % HR	24 ± 10	21 ± 7	NS
$Tmax_{HR}$	0.10 ± 0.05	0.10 ± 0.01	NS
Auc_{HR}	11 ± 21	12 ± 15	NS

Values are the mean ± standard deviation.
Auc_{HR} = area under the percent change in heart rate versus time curve; Auc_{PR} = area under the percent change in PR interval versus time curve; Max % HR = maximum percent change in heart rate; Max % PR = maximum percent change in PR interval; NS = difference not significant; $Tmax_{HR}$ = time in hours to maximum percent change in heart rate; $Tmax_{PR}$ = time in hours to maximum percent change in PR interval.

Hemodynamic and electrocardiographic variables: Hemodynamic and electrocardiographic variables were analyzed from 2 different baseline reference points. Values before calcium chloride treatment were used to evaluate calcium effects, as well as net effects of the combination. Values before verapamil treatment were used to evaluate verapamil effects. There were no statistically significant differences in baseline measurements (before calcium or verapamil) for PR interval, heart rate, systolic, diastolic or mean arterial blood pressure among any of the 3 treatment phases.

There were no statistically significant changes in mean systolic, diastolic or mean arterial blood pressure from baseline values over time during any treatment phase. Figure 1 shows the mean arterial pressures from baseline values before calcium to 2 hours after verapamil administration for all 3 treatment phases. Although not statistically significant, there was a tendency for calcium to cause small increases in mean arterial pressure and for verapamil to cause small decreases in blood pressure. The increase in mean arterial pressure owing to calcium was not evident in phase III after verapamil administration.

The PR interval was significantly prolonged in both phases (I and III) in which verapamil was administered (Figure 2). The maximal percent change in PR interval from baseline values before verapamil was 19 ± 11% during phase I and 18 ± 7% during phase III (difference not significant) (Table II). The time to maximal percent change in PR interval and the area under the percent change in PR interval versus time curve were also not significantly different between phases I and III. In both these treatment phases, PR interval returned to baseline within 2 hours. Significant changes in the PR interval were not observed after calcium-saline administration in phase II (Figure 2). Furthermore, pretreatment with calcium chloride did not alter verapamil-induced PR prolongation (Table II).

The effects of verapamil on sinus rate were evaluated using baseline values before verapamil (Table II). Verapamil administration resulted in a significant increase in heart rate ($p < 0.05$) (Figure 3). The magnitude of this increase in heart rate was similar in phase I (24 ± 10% after verapamil alone) and phase III (21 ± 7% after calcium-verapamil).

Figure 4 shows the mean percent change in heart rate observed during all 3 treatment phases using baseline values before calcium. After calcium administration, there was a significant decrease in heart rate ($p < 0.05$) in both phases II and III (Figure 4). The calcium-induced decrease in sinus rate was similar in magni-

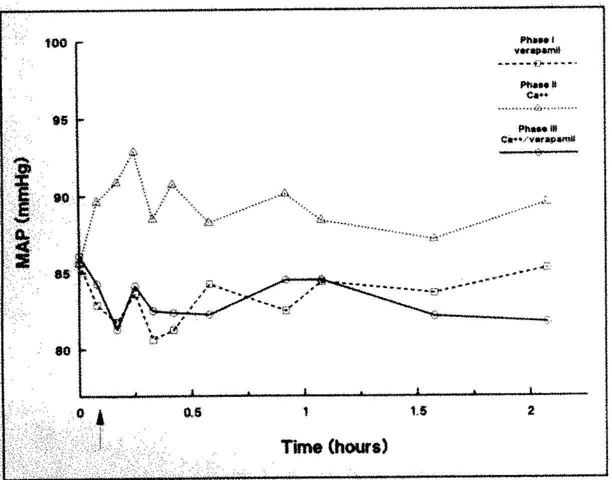

FIGURE 1. Effects of verapamil, calcium and calcium-verapamil on mean arterial pressure (MAP). Data are mean values of the 8 healthy subjects during each of the 3 treatment phases. *Time zero* is time of calcium or placebo administration. *Arrow* indicates time of administration of 10 mg of intravenous verapamil.

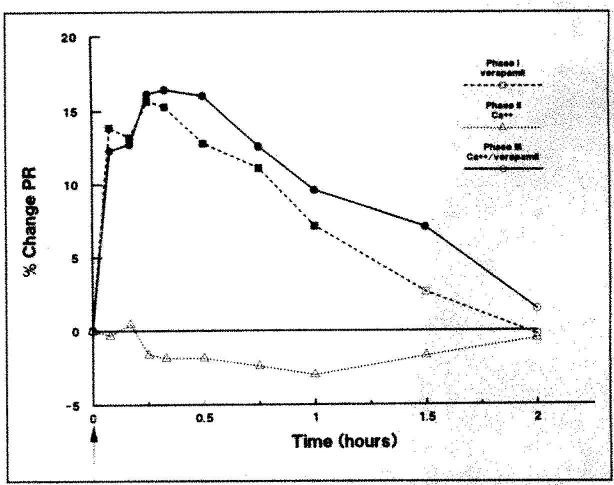

FIGURE 2. Effects of verapamil, calcium and calcium-verapamil on percent change in PR interval. Data are mean values of the 8 healthy subjects during each of the 3 treatment phases. Time zero *(arrow)* indicates administration of 10 mg of intravenous verapamil. *Dark markers* are values statistically different ($p < 0.05$) from baseline values before verapamil/saline.

tude and duration despite verapamil administration. This is demonstrated by the similar maximal percent change in heart rate, time to maximal change and area under the percent change in heart rate versus time curves in phases II and III (Table III).

The time-averaged net change in heart rate after the calcium-verapamil combination (area under the percent change in heart rate versus time curve: phase III = −23 ± 12) was significantly different ($p < 0.05$) than after verapamil alone (area under the percent change in heart rate versus time curve: phase I = 5 ± 28), when baseline values before calcium were used to evaluate the effects of the combination (Table III); that is, verapamil administration resulted in a transient increase in heart rate independent of calcium pretreatment, but this effect was offset by an initial decrease in heart rate caused by calcium in phase III. In all phases, heart rate returned to baseline values within 2 hours.

DISCUSSION

Previous studies suggest that pretreatment with intravenous calcium may attenuate the hypotensive effect of intravenous verapamil without altering its antiarrhythmic effect.[5,6,8,9] These studies were primarily conducted in patients with supraventricular tachycardias, examining reductions in ventricular response or reversion to sinus rhythm as an index of verapamil effects on atrioventricular nodal conduction. In this study, the measurement of PR interval during sinus rhythm was chosen as an objective and readily measurable reflection of the effects of verapamil on the atrioventricular node.

Pharmacokinetics: The pharmacokinetic profile of intravenous verapamil in our study is similar to that previously described.[17–19] Calcium administration did not affect the pharmacokinetics of intravenous verapamil. Therefore, the observed effect of calcium pretreatment on the actions of verapamil cannot be explained by an alteration in verapamil disposition. Unlike our study, the serum concentration versus time profile of verapamil has usually been described by a 2-compartment pharmacokinetic model.[17] The improvement in curve fit by the use of a 3-compartment model in this study is most likely a reflection of the rigorous blood sampling strategy used.

TABLE III Comparison of Heart Rate Changes Using Baseline Values Before Calcium

	Phase I (Verapamil)	Phase II (Ca^{++})	Phase III (Ca^{++}/Verapamil)	p Value
Max % HR	—	−20 ± 9	−19 ± 3	NS
$Tmax_{HR}$	—	1.11 ± 0.18	1.05 ± 0.64	NS
Auc_{HR}	5 ± 28	−21 ± 22	−23 ± 12	<0.05

Values are the mean ± standard deviation.
Abbreviations as in Table II.

Hemodynamic and electrocardiographic analysis: Verapamil administration tended to decrease mean arterial pressure, although this difference was not significant. Previous studies also report that intravenous verapamil administration has little effect on blood pressure in normotensive individuals.[20,21] In our study, the administration of intravenous calcium tended (although not statistically significantly) to increase mean arterial pressure. Similarly, Haft and Habbab[6] and Weiss et al[5] reported a small increase in mean blood pressure after administration of calcium alone. These studies also demonstrated that calcium prevented verapamil-induced hypotension in patients with supraventricular tachyarrhythmias. A calcium-induced increase in blood pressure was not evident in phase III after verapamil administration. Thus, although no major blood pressure alterations were noted in this study, the opposing action of calcium and verapamil can be appreciated.

The principal antiarrhythmic action of verapamil is to depress atrioventricular nodal conduction, which can be measured by the PR interval on the surface electro-

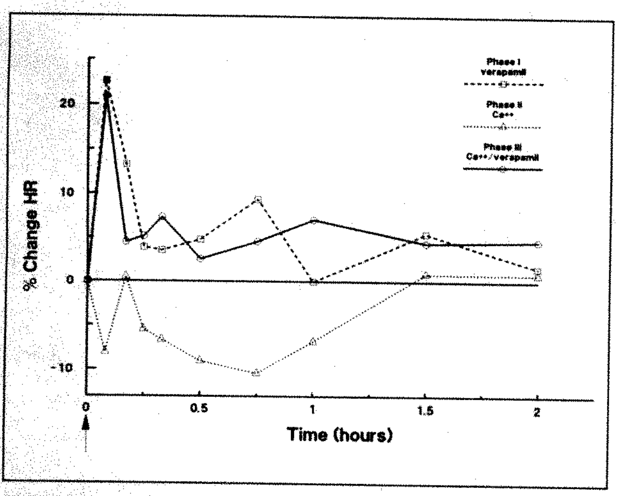

FIGURE 3. Effects of verapamil, calcium and calcium-verapamil on percent change in heart rate (HR) using the baseline values before verapamil/saline. Data are mean values of the 8 healthy subjects during each of the 3 treatment phases. Time zero *(arrow)* indicates administration of 10 mg of intravenous verapamil. *Dark markers* are values statistically different (p <0.05) from baseline values before verapamil/saline.

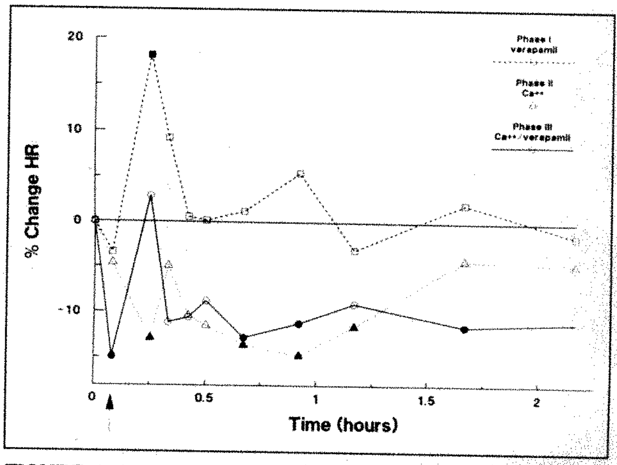

FIGURE 4. Effects of verapamil, calcium and calcium-verapamil on percent change in heart rate (HR) using the baseline values before calcium/saline. Data are mean values of the 8 healthy subjects during each of the 3 treatment phases. *Time zero* is time of calcium or placebo administration. The *arrow* indicates administration of 10 mg of intravenous verapamil. *Dark markers* are values statistically different (p <0.05) from baseline values before calcium/saline.

cardiogram. PR interval prolongation occurs with both oral and intravenous verapamil[1,22,23] and can be correlated with serum verapamil concentration.[17-19,23,24] As anticipated, verapamil administration resulted in a significant prolongation of the PR interval. Importantly, calcium administration did not alter PR prolongation resulting from verapamil administration. Most of the published studies that examine this drug combination suggest that calcium will not reverse or prevent the antiarrhythmic effects of verapamil.[5,6,9,10,25] However, 3 studies of dogs report that calcium can reverse the atrioventricular nodal effects of verapamil.[11,26,27] Lang et al[26] found that an increase in serum calcium to 5 mmol/liter was effective in reversing the verapamil-induced impairment of atrioventricular nodal conduction. Hariman et al[11] found that extreme elevations in serum calcium (from a mean concentration of 4.6 to 8.2 mEq/liter) were necessary to reduce verapamil-induced atrial-His interval prolongation significantly. Interestingly, this latter study[11] demonstrated that an even greater increase in serum calcium (to a mean concentration of 10.2 mEq/liter) actually prolonged the atrial-His interval. Our results in humans show that in clinically used doses, pretreatment with calcium will probably not interfere with the antiarrhythmic efficacy of verapamil.

Calcium administration produced a significant decrease in heart rate in our subjects. This effect was seen shortly after calcium administration and persisted for approximately 1 hour. Although a decrease in heart rate after intravenous calcium administration has previously been reported,[6,28] the mechanism(s) remains unclear; one may postulate either a direct or reflex mechanism.[25] Verapamil had the opposite effect, i.e., an increase in heart rate, probably by a reflex mechanism. Other investigators[20] also observed a brief increase in heart rate with no significant change in blood pressure after intravenous verapamil. Verapamil administered after calcium increased heart rate above baseline values before verapamil by a similar magnitude as that observed when verapamil was administered alone. However, pretreatment with calcium counteracted the ability of verapamil to cause a net increase in heart rate. Therefore, the lack of an overall verapamil-induced increase in heart rate in phase III can be attributed to an initial decrease in heart rate caused by the calcium pretreatment. These findings imply that the sensitivity of the sinus node to respond to reflex increases in sympathetic tone is unaltered by calcium.

In each phase of this study, differing effects of calcium and verapamil were noted. Calcium, in the doses used, caused a small increase in blood pressure and a decrease in heart rate but did not affect atrioventricular conduction. Verapamil caused a small decrease in blood pressure, an increase in heart rate, probably because of a reflex increase in sympathetic tone secondary to vasodilation, and a marked delay in atrioventricular conduction, which was not affected by increases in sympathetic tone. Calcium pretreatment countered this verapamil-induced reflex increase in heart rate, but left the degree of PR prolongation unaltered. In this study, calcium and verapamil appear to produce opposing effects on the sinus rate and arterial blood pressure, but not on atrioventricular conduction.

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Patterns of ST-Segment Change During Acute No-Flow Myocardial Ischemia Produced by Balloon Occlusion During Angioplasty of the Left Anterior Descending Coronary Artery

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An early manifestation of acute myocardial ischemia is the development of ST-segment and T-wave changes. Clinical decisions for treatment are based on ST-segment shifts on the surface electrocardiogram (ECG). ST-segment depression is believed to represent subendocardial involvement, with less extensive myocardial injury. ST-segment elevation reflects transmural involvement, with greater extent of myocardial injury.[1-3] ST-segment depression is generally induced by factors that increase myocardial demand, such as atrial pacing or exercise stress, whereas ST-segment elevation is induced by near total cessation of coronary blood flow.

After acute total occlusion of the vessel, myocardial injury is believed to progress from the endocardium to the epicardial layers. Thus, we would expect to observe ST-segment depression progressing through an isoelectric point to ST-segment elevation. This may explain why some patients have no significant changes on the ECG when presenting with an acute myocardial infarction. To test this hypothesis in humans, we used balloon angioplasty of the coronary arteries as the model for acute no-flow ischemia. Intracoronary electrograms were obtained from the center of the ischemic zone by attaching the proximal end of the balloon angioplasty guidewire to the V_1 lead on the surface ECG. Patterns of ST-segment responses on the intracoronary electrogram and surface leads II and V_5 were continuously recorded.

We studied 35 patients (19 men, 16 women, mean age ± standard deviation 58 ± 12 years) during balloon dilatation of the left anterior descending coronary artery. All patients were receiving antianginal medications (20 nitrates, 22 calcium antagonists and 12 β blockers; mean 1.9/patient [range 1 to 3]) and also received aspirin, diazepam and diphenhydramine hydrochloride before the procedure. None of the patients was receiving digoxin.

Left ventriculography and coronary angiography were performed in the usual fashion within 1 week of the study. Analysis of left ventricular wall motion and ejection fraction was obtained from the 30° right anterior oblique projection. Coronary angiography was performed in multiple views. The presence and degree of collateral filling of the left anterior descending artery were assessed from angiograms obtained during contrast injection of the right coronary artery performed before balloon angioplasty, using the method described by Rentrop et al.[4]

Guiding catheters for balloon angioplasty were placed in the usual manner, using the Judkins technique. After initial angiography and identification of the target lesion, a 0.014-inch diameter, high-torque, floppy, steerable guidewire (ACS, Inc) was positioned in the distal left anterior descending coronary artery. The proximal end of the guidewire was connected to the V_1 *lead of the standard electrocardiograph in order to record a local unipolar intracoronary electrogram from myocardium distal to the stenosis to be dilated. The intracoronary electrograms were continuously recorded with a 35-Hz low-pass filter and a standard electrocardiograph (Marquett, Inc). Leads II and* V_5 *were also monitored. In all patients, baseline recordings were obtained before balloon inflation. The angioplasty balloon catheter was then advanced and positioned at the stenosis. The number of balloon inflations, duration of each inflation and the pressures used were determined by the operator, based on the angiographic appearance of the vessel before and after each inflation. A unipolar intracoronary electrogram and body surface leads II and* V_5 *were recorded during each balloon inflation* ≤ 120 *seconds and until the electrocardiographic signal returned to baseline after balloon deflation. The duration of each balloon inflation was based on patient symptoms and blood pressure values. The unipolar electrograms and body surface ECGs were evaluated for patterns of ST-segment deviation. The maximal ST-segment deviation was determined 80 ms after the J point on the intracoronary and surface ECGs.*

Data are reported as mean ± standard deviation. Comparison of discrete variables was made using the paired t *test. A p value <0.05 was considered statistically significant.*

A previous myocardial infarction was documented in 20 patients and 12 patients had wall motion abnormality (8 severe, 4 mild hypokinesis) in the distribution of the left anterior descending coronary artery. No patient had an akinetic or dyskinetic anterior segment. Intracoronary collateral vessels to the left anterior descending artery were evident during injection of the right coronary artery in 11 patients (grade 3 in 4, grade 2 in 4, grade 1 in 3 patients).

During dilatation of the left anterior descending artery, 30 patients developed chest pain. ST-segment deviations on the intracoronary electrograms were evident in 33 patients (94%). On the intracoronary electrograms, only ST-segment elevation developed in 30 patients. The mean ST-segment elevation was 9 ± 7 mm (range 1 to

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25) (Figure 1). Only 2 patients developed ST-segment depression that then progressed to ST-segment elevation, traversing through an isoelectric point during single-balloon inflation (Figure 2). One patient developed only ST-segment depression of −3 mm.

There were no clinical or angiographic variables that distinguished the 3 patients who had ST-segment depression or no change on the intracoronary electrogram from patients who developed only ST-segment elevation. The ejection fraction, wall motion, and the presence or absence of collateral vessels were similar in the 2 groups. Likewise, there was no obvious difference between the 2 patients in whom ST-segment depression progressed to ST-segment elevation and the remaining patients who had only ST-segment elevation. The 11 patients who had angiographic collateral vessels to the left anterior descending artery had significantly less ST-segment elevation than those without collateral vessels (4 ± 4 vs 12 ± 6 mm [p <0.001], respectively).

During dilatation, ST-segment changes developed on the surface ECG in only 13 patients (37%) (elevation 11, depression 2). The mean ST-segment elevation on the surface ECG in the 11 patients was 2 mm (range 1 to 4). No patient showed a transition from ST-segment depression to ST-segment elevation on the surface ECG. All these patients also had significant ST-segment elevations on the intracoronary electrograms.

Our results show that the sensitivity of intracoronary electrograms for the detection of myocardial ischemia during brief episodes of no-flow ischemia is much greater than surface leads. Thirty-three patients (94%) had ST-segment deviations during balloon inflation on the intracoronary ECG, but only 13 patients (37%) had ST-segment changes on surface leads (p <0.001). This is consistent with our previous findings[5] and those of Friedman et al.[6] Because all 12 surface electrocardiographic leads were not monitored, it is possible that some patients may have had undetected ST-segment deviations. The presence of collateral vessels resulted in less ST-segment change on the intracoronary electrogram (4 vs 12 mm), suggesting a smaller ischemic zone. We cannot exclude the possibility that some patients may have recruited collateral vessels during balloon angioplasty. Our findings of greater ST-segment elevation on the intracoronary ECG than on the surface leads (9 vs 2 mm) is consistent with findings in animal studies that show a significant decline in the magnitude of recorded potentials with increasing distance between the heart and the recording leads.[7,8]

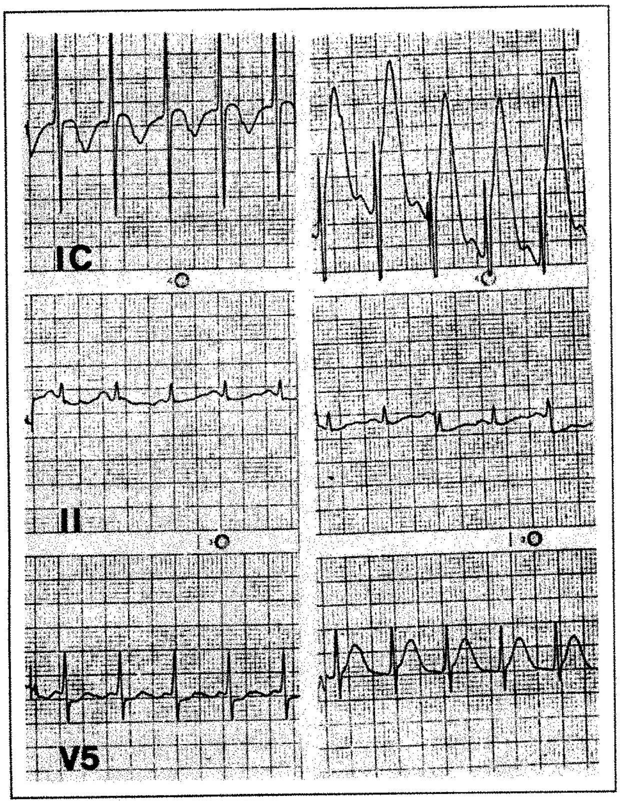

FIGURE 1. Intracoronary electrogram (IC) and surface leads II and V$_5$ during baseline *(left)* and dilatation *(right)* showing 10-mm ST-segment elevation. There was no ST-segment depression.

Previous studies in normal canine hearts have characterized in detail the relation between intracellular action potential and extracellular electrograms recorded from these regions.[9,10] There is also a thin layer of endocardial tissue that is protected from ischemia by the presence of left ventricular chamber blood, which acts both as an oxygen source and a diffusion pathway for metabolites.[11] As a result, during subendocardial ischemia, a thin layer of endocardial tissue is created, which is surrounded by nonischemic tissue on all sides. Holland and Brooks[12] described the theory of TQ- and ST-segment changes induced by myocardial ischemia. They identified spatial (ischemic area and shape, electrode location) and nonspatial factors (electrolytes, heart rate, drugs) that combine to create the direction of TQ- and ST-segment

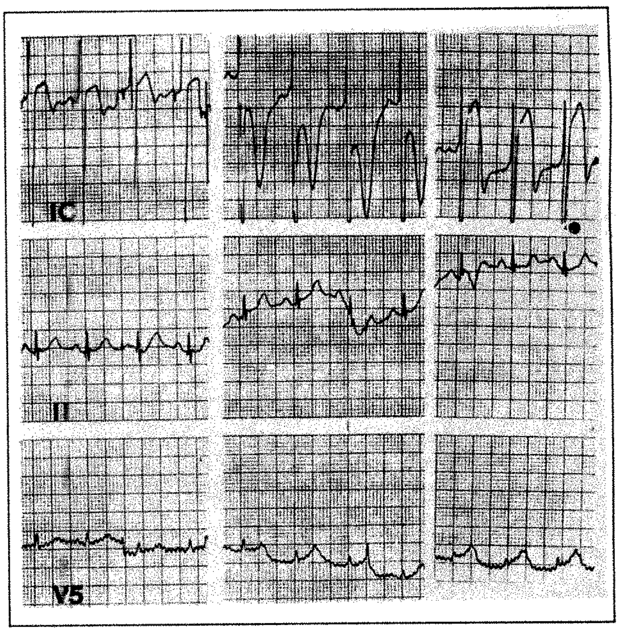

FIGURE 2. Intracoronary electrogram (IC) and surface leads II and V$_5$ during baseline *(left)*. First ST-segment depression *(middle)* is followed by ST-segment elevation *(right)* during dilatation.

changes between the myocardial and body surface.[13] The direction of the ST-segment changes on the epicardium and the body surface electrocardiographic leads will depend on the magnitude and the direction of the injury currents. In the setting of low-flow ischemia created by an increased oxygen demand because of stress or atrial pacing, the body surface leads characteristically demonstrate TQ-segment elevation and ST-segment depression, because of the voltage difference between the subendocardial and epicardial regions. With progression of ischemia to the epicardial layer, the magnitude and direction of the injury current change on the body surface leads characteristically reveal TQ-segment depression and ST-segment elevation.[12,14]

We therefore expected to see a transition from ST-segment depression to elevation as the wave front of ischemia progressed from endocardial to epicardial layers in this human model of acute no-flow ischemia. Only ST-segment elevation was present in 30 patients, indicating that the magnitude and direction of the injury currents are such that only TQ-segment depression and ST-segment elevation occurs. In those 2 patients in whom no ST-segment change was noted on the epicardial electrogram, it is possible that only mid-myocardial ischemia developed because of the presence of a nonischemic subendocardial layer protected by left ventricular cavity blood and the epicardial layer, resulting in a balance between those factors generating TQ-segment elevation and ST-segment depression and those generating the reverse changes.

Our inability to detect a transition may be because of the instantaneous development of transmural ischemia in humans or because of the presence of a nonischemic endocardial layer, which results in simultaneous progression of ischemia to the epicardium and endocardium, resulting in only ST-segment elevation.

Acknowledgment: We wish to thank the technologists in the cardiac catheterization laboratory for their assistance.

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Doppler Echocardiographic Findings in Normal-Functioning St. Jude Medical and Björk-Shiley Mechanical Prostheses in the Tricuspid Valve Position

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The difficulties of performing a conventional hemodynamic study in patients with a mechanical prosthesis implanted in the tricuspid valve position make the Doppler method a useful, evaluative tool. However, the amount of available Doppler data in this field is scarce.[1,2] We report Doppler echocardiographic findings in 16 patients with clinically normal-functioning mechanical prostheses in the tricuspid valve position.

We prospectively studied 17 consecutive female patients, aged 46 ± 10 years (range 27 to 63), who underwent tricuspid valve replacement because of rheumatic heart disease (15 patients), Ebstein's anomaly (1 patient) and surgical iatrogenic injury of the tricuspid valve (1 patient). The prostheses had been implanted between 9 months and 15 years (mean 4.3) before the Doppler study was performed. St. Jude prostheses were implanted in 9 patients and Björk-Shiley in 8. Atrial fibrillation was present in 14 patients, sinus rhythm in 2 and a paced rhythm in 1.

To assess whether the prosthesis functioned normally before the Doppler study, each patient underwent a complete physical examination, 12-lead resting electrocardiography, chest x-ray, and M-mode and 2-dimensional echocardiography. In 1 patient with a Björk-Shiley valve, the presence of clinical and echocardiographic signs of prosthetic obstruction led to a fluoroscopic examination, which showed an incomplete opening of the

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TABLE I Clinical and Doppler Echocardiographic Findings in 16 Patients with a Tricuspid Prosthetic Valve

Pt. No.	Age (yr)	Time from Insertion (yr)	Size	Mean DG (mm Hg)	Peak V (m/s)	PHT (ms)
			St. Jude			
1	53	2	25	2.0	1.24	167
2	60	4	27	4.0	1.10	85
3	59	4	27	4.0	1.50	124
4	41	4	31	3.3	1.30	100
5	35	4	31	5.0	1.50	—
6	51	2	31	2.0	1.15	70
7	63	2	31	3.0	1.50	110
8	42	2	31	5.0	1.60	120
9	53	2	31	1.0	0.85	40
			Björk-Shiley			
10	36	1	25	7.0	1.70	150
11	46	7	25	6.0	1.80	270
12	44	5	27	3.0	1.60	90
13	52	10	31	7.0	1.80	220
14	35	0.9	31	5.0	1.40	—
15	27	9	31	2.5	1.52	120
16	37	10	31	5.0	1.50	290

Mean DG = mean diastolic gradient; Peak V = peak velocity; PHT = pressure half-time; — = no information.

disc. This patient was excluded from the study. The remaining patients were in New York Heart Association functional class I.

The Doppler study was performed with a cardiac ultrasound imaging unit (Vingmed CFM-700) equipped with a 3.5-MHz transducer. A continuous-wave Doppler study of the flow velocities across the tricuspid prosthesis was performed either from the apical or the precordial approaches, depending on where the optimal flow profile was obtained. Adequate alignment between the blood flow and the ultrasound beam was obtained with the aid of color-flow Doppler.

The following Doppler measurements were obtained: diastolic maximal flow velocity, mean diastolic pressure gradient, using the simplified Bernoulli's equation of transprosthetic flow velocity, and pressure half-time. All Doppler recordings were obtained during a period of postexpiratory apnea and 3 different cardiac cycles were analyzed to obtain an average value. Detection of regurgitant prosthetic flow was attempted by means of either continuous-wave Doppler or color-flow mapping. As part of routine follow-up, a second Doppler echocardiographic study was performed in 12 patients within a mean interval of 10 months (range 4 to 13) after the first examination.

Comparison between Doppler results in patients with St. Jude and Björk-Shiley prostheses was performed by means of an unpaired t *test and between the first and long-term examinations by means of a paired* t *test. A p value <0.05 was considered statistically significant. Values are expressed as the mean ± standard deviation.*

Adequate transprosthetic flow Doppler recordings were obtained in all patients. The results of the first examination are listed in Table I.

In patients with a St. Jude prosthesis, mean diastolic pressure gradient ranged from 1 to 5 mm Hg (mean 3.26 ± 1.39), peak velocity from 0.85 to 1.6 m/s (mean 1.30 ± 0.24) and pressure half-time from 40 to 167 ms (mean 102 ± 38). Mild tricuspid regurgitation was detected in 1 patient (no. 6). In patients with a Björk-Shiley prosthesis, mean diastolic gradient ranged from 2.5 to 7 mm Hg (mean 5.07 ± 1.8), peak velocity from 1.4 to 1.8 m/s (mean 1.62 ± 0.16) and pressure half-time from 90 to 290 ms (mean 188 ± 84). No regurgitations were seen.

The results obtained in the 12 patients who were reexamined showed no significant differences from the values obtained at the first study. New regurgitations were not detected, nor were the clinical signs suggestive of malfunction.

Invasive hemodynamic values in patients with tricuspid valve prostheses have rarely been reported because of the inconvenience of these procedures. In 1966 Bristow et al[3] reported on 12 patients with normal-functioning Starr-Edwards tricuspid prostheses, finding a 4.7 ± 2 mm Hg average mean diastolic gradient (range 3 to 9). Values between 3 and 7 mm Hg were noted in the few patients with normal Björk-Shiley tricuspid prostheses studied.[2] Invasive hemodynamic data are also scarce for patients with thrombosed tricuspid prostheses; Thorburn et al[4] found mean gradients ranging from 5 to 18 mm Hg (mean 11 ± 4) in 8 patients.

Doppler echocardiography has been shown to be useful in the detection of malfunctioning mechanical and biologic tricuspid valves,[2,5] but data on normal-functioning prostheses in this position are rare. In our series of patients, Doppler-determined tricuspid mean gradients (1 to 7 mm Hg) are in the same range as those determined by invasive procedures.[1,2] These values of diastolic gradients may seem relatively high for a valve in the tricuspid position, because pressure gradients in patients with moderate native tricuspid stenosis are within the same range. This is to be expected, however; assuming the absence of an intracardiac shunt, the pressure gradient must be the same for the same prosthesis, implanted either at the tricuspid or mitral position, where gradients within the range reported here are usual.

Prolonged values of Doppler pressure half-time in obstructed Björk-Shiley tricuspid prosthetic valves have been reported by Pye et al.[6] Their results suggest that, in the absence of significant valve regurgitation, a pressure half-time >200 ms, together with a peak diastolic velocity >1.6 m/s, indicate tricuspid prosthetic obstruction. Nevertheless, in our series, 2 patients (numbers 10 and 13) fulfilled these criteria, but no clinical signs or symptoms suggesting prosthetic dysfunction were present. The longest pressure half-time value obtained from among our clinically normal-functioning tricuspid prostheses was 290 ms, whereas the pressure half-time of the single patient with an obstructed prosthesis, initially excluded from our series, was 470 ms.

The average mean diastolic pressure gradient, peak velocity and pressure half-time were significantly lower in patients with St. Jude prostheses than in those with Björk-Shiley valves. These results concur with the differing hemodynamic profiles of these valves, which favor the St. Jude model in terms of effective orifice area and residual diastolic gradient.

A second Doppler examination was performed in most patients (12 of 16) at follow-up after a mean of 10 months. There were no significant differences between the first and second determinations in the whole group, confirming the good reproducibility of the Doppler technique in the follow-up of prosthetic valve function.

In conclusion, normal-functioning tricuspid mechanical prostheses exhibit Doppler diastolic mean gradients ≤ 7 mm Hg and pressure half-time values ≤ 290 ms. Doppler values are fairly constant at repeat examinations. Patients with Björk-Shiley prostheses have slightly higher gradients and longer pressure half-times than those with St. Jude valves. A routine basal examination of patients with prosthetic valves by Doppler echocardiography will permit the assessment of any increase in the pressure gradient or half-time, thus allowing the detection of a potential dysfunction of the prosthesis.

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Correlation of the Physiologic Parameters of a Continuous Ramp Versus an Incremental James Exercise Protocol in Normal Children

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Until recently, all clinically available exercise protocols involved steady-state or incremental increases in work load.[1] In these protocols, the subject exercises against a predetermined and unchanging work load or exercises with the work load increasing in a continuous stepwise fashion. These protocols were designed so that the subject would be at or near steady state when physiologic parameters were measured. This was especially important in the past when only a limited number of points by Douglas bag collection of respiratory gases were obtainable to assess the patient's physiology. Today, with the use of computer systems interfaced to rapid gas analyzers, this limitation in the number of data points collected no longer exists. However, the small number of work loads assessed and the size of the step increments limit these protocols. These limitations are especially significant in small children or children with moderate to severe exercise intolerance. By starting at zero watts (unloaded pedalling) and continuously increasing the work load in small increments, a ramp protocol alleviates these problems. The ramp protocol, however, introduces a new problem. The patient is never at a steady state when physiologic parameters are measured. To assess the effects of a non–steady-state exercise protocol on physiologic parameters, we compared the responses of normal children to both a continuously increasing non–steady-state ramp protocol and the standard incremental "steady state" James[2-4] protocol.

We evaluated 20 normal subjects (8 boys and 12 girls), ages 6 to 16 years (mean ± standard deviation 10.7 ± 2.6 years) using both a continuously increasing non–steady-state ramp protocol and an incremental steady-state James protocol. The height of the children ranged from 109 to 161 cm; weight ranged from 19 to 54 kg; and body surface area ranged from 0.8 to 1.6 m^2. *The study population included healthy siblings of patients with congenital heart disease at the Children's Hospital of Philadelphia, and normal school children. The subjects were not highly conditioned nor engaged in regular athletic endeavors to better represent our normal pediatric population.*

The order of the exercise protocols was randomized, with 10 subjects performing the continuously increasing non–steady-state ramp protocol first and 10 subjects

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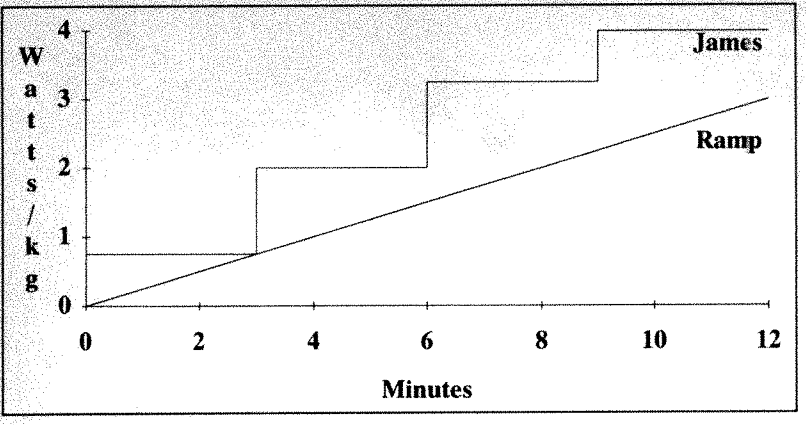

FIGURE 1. Comparison of the work load increments for the ramp and James protocols.

TABLE I Mean ± Standard Deviation of the Ramp and James Protocols at Rest and Maximum Exercise

Physiologic Parameters	Rest Ramp	 James	Maximum Exercise Ramp	 James
Heart rate (beats/min)	91 ± 8	90 ± 13	192 ± 10	187 ± 14*
Systolic blood pressure (mm Hg)	109 ± 12	108 ± 10	147 ± 16	138 ± 17
Diastolic blood pressure (mm Hg)	60 ± 6	62 ± 7	67 ± 7	64 ± 10
Respiratory rate (breaths/min)	24 ± 8	22 ± 8	57 ± 14	51 ± 11*
Tidal volume (liters)	0.50 ± 0.18	0.51 ± 0.25	1.03 ± 0.40	1.04 ± 0.40
Minute ventilation (liters)	10.8 ± 1.8	9.8 ± 2.1	54.6 ± 15.9	50.1 ± 15.2
Oxygen consumption (liters/min)	0.22 ± 0.06	0.22 ± 0.07	1.11 ± 0.44	1.09 ± 0.43
Carbon dioxide production (liters/min)	0.19 ± 0.05	0.19 ± 0.07	1.24 ± 0.55	1.24 ± 0.54
Ventilatory equivalent for oxygen	54 ± 23	48 ± 12	53 ± 13	49 ± 11
Ventilatory equivalent for carbon dioxide	59 ± 21	57 ± 16	44 ± 29	40 ± 28
Respiratory quotient	0.88 ± .014	0.86 ± 0.10	1.09 ± 0.1	1.11 ± 0.1
Arterial oxygen saturation (%)	98 ± 1	98 ± 2	96 ± 2	96 ± 3
Cardiac index (liters/min/m^2)	4.3 ± 0.9	4.2 ± 1.0	8.5 ± 1.3	8.6 ± 1.2
Stroke volume index (ml/beat/m^2)	48 ± 10	48 ± 12	47 ± 7	48 ± 7
Systemic vascular resistance index (U·m^2)	18 ± 4	19 ± 6	11 ± 2	11 ± 1

* $p < 0.05$ between ramp and James protocols at equivalent states.
U = wood units.

performing the incremental steady-state James protocol first. The median interval between performance on the 2 cardiopulmonary exercise tests was 10 days. We instructed the subjects not to eat for 2 hours before the exercise tests. Upon arriving at the Cardiopulmonary Exercise Lab, we obtained a brief history from the subject and guardian to assure that there were no contraindications to a cardiopulmonary exercise test. We then explained the equipment and procedure to both the parent and subject and obtained informed consent. Subjective estimates of exercise tolerance and baseline activity level were assessed using a standardized questionnaire. The parent was then asked to wait outside the exercise laboratory while the subject performed the test.

Before the subject's first exercise test, we measured the subject's flow volume loop, slow vital capacity and maximal voluntary ventilation by spirometry.

We used a Medical Graphics CPE 2000 cycle ergometer for all the exercise tests. For the ramp protocol, the work load increased 0.025 W/kg every 6 seconds. This resulted in a 1-watt increase in work load every 6 seconds for our average patient. In the James protocol, the work load increased incrementally every 3 minutes as defined by James et al (2–4). Figure 1 illustrates the differences in work loads for the 2 protocols for a typical patient weighing 40 kg. Work load increases more slowly in the ramp than James protocol so that at 10 minutes a patient is working at 3 W/kg on the ramp protocol and 4 W/kg on the James protocol. An IBM compatible personal computer interfaced to the cycle ergometer through a digital-to-analog converter controlled the work rate. We continuously monitored the subject's heart rate and rhythm using a Marquette Case 12 exercise electrocardiogram system. The Marquette Case 12 recorded a 12-lead electrocardiogram before exercise and every 3 minutes during exercise. We computed heart rate by averaging the interval between 2 complete RR cycles. We monitored blood pressure using a stethophonic microphone taped over the left brachial artery and a standard mercury manometer. A Paramed 9300 automated blood pressure system controlled cuff inflation and deflation. We recorded the pressure levels at the first and fourth Korotkoff sounds representing systolic and diastolic pressures, respectively. An Ohmeda Biox 3700 ear oximeter recorded oxygen saturation throughout exercise. A Perkin Elmer MGA 1100 mass spectrometer continuously measured respiratory oxygen and carbon dioxide partial pressures. We calibrated the mass spectrometer with analyzed gases before each exercise test. A Sensormedics turbine transducer located distal to the subject's *mouthpiece measured ventilatory flow. An acetylene-helium-carbon monoxide rebreathing technique*[5] *measured cardiac index at rest and every 3 minutes throughout exercise. We calculated stroke volume index by dividing cardiac index by heart rate and systemic vascular resistance index by dividing cardiac index by mean arterial blood pressure. We determined ventilatory anaerobic threshold using the V-slope method.*[6,7] *This technique involves 9-second averaging of breath-by-breath oxygen consumption and carbon dioxide production data. Carbon dioxide production is then plotted against oxygen consumption. A computerized regression analysis then determines the first and second components of the oxygen consumption-carbon dioxide production response and solves for the intercept. This intercept is the ventilatory anaerobic threshold.*

All subjects were verbally encouraged to continue exercising until exhaustion. After exercise, we helped the subjects off the cycle ergometer and monitored blood pressure, heart rate and electrocardiogram for another 10 minutes.

The physiologic parameters were compared using paired student's t *test and linear regression. All data are expressed as mean ± standard deviation unless otherwise noted.*

Table I lists the mean values and standard deviations of the physiologic parameters of the ramp and James protocols at rest and peak exercise. At rest there were no significant differences in any of the parameters we analyzed indicating good test retest correlation. At peak exercise, maximum heart rate and respiratory rate were significantly higher on the ramp than on the James protocol. At peak exercise there were no differences in the mean values between the ramp and James protocols for tidal volume, minute ventilation, oxygen consumption, carbon dioxide production, arterial oxygen saturation, cardiac index, stroke volume index or systemic vascular resistance index. Table II lists the data for total exercise time, total work, mean power, maximum power and ventilatory anaerobic threshold. The ramp protocol's maximum power was 10% and total work was 18% higher than that of the James protocol. Consistent with the longer exercise time of the ramp protocol and the more gradual slope, the mean power on the ramp protocol was 18% lower than that of the James protocol.

We successfully identified the ventilatory anaerobic threshold 60% of the time using the V-slope method. There were no significant differences in ventilatory anaerobic threshold between the ramp and James protocols. Since work loads increased every 3 minutes on the James protocol and since we measured cardiac output 2.5 minutes into each work load, we averaged the physiologic parameters for the period of 2.0 to 2.5 minutes into each work load. During this period, the child should be at or nearly at steady state. We then assessed the child's ramp protocol to find the 30-second period in which average work load matched that of the James protocol. We used a paired t *test to compare physiologic parameters at these equivalent work loads. Although there were minor differences in these mean values, none of the differences was statistically significant. There was a strong correlation between the values from the ramp and James protocols at equivalent work loads with correlation coefficients ranging from 0.68 for minute ventilation to 0.87 for carbon dioxide production.*

TABLE II Exercise Tolerance: Ramp Versus James Protocol

	Ramp	James
Exercise time (min)	9.4 ± 3.3	6.2 ± 2.9*
Total work (KJ)	28.3 ± 23.5	23.2 ± 17.9
Mean power (W)	44.2 ± 22.0	54.3 ± 18.8*
Maximum power (W)	87.6 ± 43.8	79.8 ± 39.2*
Ventilatory anaerobic threshold (liters/min)	0.80 ± 0.14	0.75 ± 0.18

* $P < 0.05$ between ramp and James protocols.

Although blood pressure and cardiac outputs were measured every 3 minutes during exercise, these measurements frequently did not occur at equivalent work loads for the 2 protocols. Thus, we could not compare these 2 measurements at equivalent intermediate work loads.

To assess the effects of non–steady-state exercise and to develop an exercise protocol for the assessment of children with moderate to severe exercise intolerance we compared the physiologic parameters obtained from a continuously increasing non–steady-state ramp protocol with those from a 3-minute incremental steady-state protocol. Unlike previous studies using a ramp protocol in which a constant ramp slope was used,[1,8–10] we elected to index our ramp slope to the patient's weight. This allowed us to use the same protocol across a wide range of patient ages and sizes and alleviated the problem of having to validate multiple ramp slopes for various sizes of children. A normal child should be able to work at approximately 3 W/kg at peak exercise.[11] To collect 10 to 12 minutes of data on each child we chose a ramp slope of 0.25 W/kg/min. This results in a 3 W/kg work load 12 minutes into the exercise protocol. The 3 W/kg maximum was an overestimate for our average nonconditioned child as the mean work load at peak exercise in this study was 2.4 W/kg. This still allowed for 9.4 minutes of data collection in the average child on the ramp protocol compared with 6.2 minutes on the standard James protocol. Thus, the ramp slope chosen for this study is suitable for clinical exercise testing.

It has been stated that one must be at a steady state to measure physiologic parameters accurately.[12,13] If this were true, a ramp protocol, in which the subject is never at steady state, would be unacceptable. Our results, however, prove that there is no difference in physiologic parameters between the standard steady state James protocol and our non–steady-state ramp protocol. This finding supports a study done by Whipp et al[1] that found that aerobic parameters can be reliably determined during exercise regardless of whether a ramp, steady-state incremental or a constant load protocol was used. Because we detected no physiologic differences between the steady-state and non–steady-state protocols indicate that the time constants of the physiologic responses are short enough that the responses can keep up with the ramp protocol's gradual increase in work load. The only differences between the 2 protocols occur at peak exercise. It is expected that, in an incremental steady-state protocol, some patients, while unable to sustain exercise at the next work load of the protocol, would be capable of sustaining exercise at an intermediate work load between their current work load and the next full step increase of the incremental protocol. Indeed, the maximum power on the ramp protocol was 10% higher than the maximum power on the James protocol. Thus, it is not unexpected that some indexes, such as maximum heart rate, were also significantly higher on the ramp protocol than on the James protocol. Because the ramp protocol's work load increases at a slower rate than the James protocol, it takes a longer time to reach comparable work loads. This explains why the patient's exercise time is longer and their mean power is lower on the ramp than on the James protocol. The longer exercise time, spent at lower subanaerobic work loads accounts for the greater total work performed on the ramp than on the James protocol. Once the patient reaches their maximum oxygen consumption, further increases in work load have no effect on oxygen consumption. Thus, the oxygen consumptions at peak exercise oxygen are similar for the 2 protocols.

We obtained the ventilatory anaerobic threshold in 60% of our subjects (Table II). Although we thought that the ramp protocol, with its continuously increasing work load, would allow a more precise determination of ventilatory anaerobic threshold than the James protocol, there were no significant differences in the ventilatory anaerobic thresholds between the 2 protocols.

Although one goal of this study was to develop a more appropriate exercise protocol for the testing of children with moderate to severe limitations in their exercise tolerance, we did not include such children in this study. We believe that, without a better understanding of the normal response to a ramp protocol, it would be difficult to assess the response of children with moderate to severe limitations in their exercise tolerance. Thus, it would not be ethical to subject these children to 2 maximal cardiopulmonary exercise tests. Having established this protocol in normal children and having proved that, at least in normal children, there is no significant difference between a steady-state and non-steady-state exercise protocol, we believe it reasonable to conclude that the non-steady-state ramp protocol would be preferable in children with moderate to severe exercise intolerance. Further study of such children is necessary to prove this definitively.

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Risk of Dysphagia After Transesophageal Echocardiography

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Karl Krieger, MD, O. Wayne Isom, MD, and Richard B. Devereux, MD

Transesophageal echocardiography (TEE) allows evaluation of cardiac, valvular and vascular structure and function in a relatively noninvasive manner. Although sustained esophageal pressure during intraoperative monitoring might possibly cause injury to the mucosa or deeper layers, reports of complications related to the technique are rare. Cucciara et al[1] reported laryngeal injury after TEE monitoring in the sitting position. Urbanowicz et al[2] found no histologic esophageal damage in dogs after maximum surface contact pressure between the esophagus and a fully flexed TEE probe. After several patients complained of dysphagia after cardiac surgery, we identified by prospective interviews 20 patients who had dysphagia postoperatively.

A total of 20 patients were identified as having postoperative dysphagia from January 1, 1987, through May 31, 1988. The charts of these patients were reviewed. Four patients had undergone TEE; 16 had not. During this period, 1,245 adult cardiac operations that required cardiopulmonary bypass were performed. Of these, 217 were monitored with TEE. The distribution of cardiac operations is summarized in Table I. The chi-square test revealed no difference in the incidence of dysphagia between patients who underwent cardiac surgery with and without monitoring by TEE ($p > 0.9998$).

Dysphagia is a symptom that may be a manifestation of such diverse syndromes as esophagitis, stricture, esophageal achalasia or perforation. "Stress" associated with neurologic disease or after operations or burns remote from the esophagus has been implicated in noninstrumental perforation of the esophagus.[3] The incidence of complications with fiberoptic peroral endoscopy used to diagnose gastrointestinal disorders has been estimated to be 0.1 to 0.2%, and mortality from the use of these instruments has been reported to between 0.14 and 0.65 per 1,000 procedures.[4]

No complications to date have been reported after intraoperative TEE monitoring in supine patients, but transient postoperative laryngeal dysfunction has been reported in 2 neurosurgical patients monitored by TEE during surgery in the sitting position.[1] We report 20 patients who experienced at least mild dysphagia after cardiac surgery. There was no difference in the incidence of dysphagia between the group of patients who had TEE monitoring and those who did not.

Because of the concern over probe-induced thermal injury, we turn the unit off during bypass and use the minimal gain and power output settings to obtain acceptable pictures.

Certain limitations of this study deserve comment. Patients having dysphagia were identified both prospectively and by a retrospective chart review based on complaints of dysphagia made in the postoperative period. No information is available concerning the prevalence of dysphagia preoperatively, and our report is based on the occurrence of dysphagia, a symptom of varying cause and severity, rather than on objective tests of esophageal function. The frequent occurrence of discordances between dysphagia or other symptoms and measures of esophageal dysfunction has recently been documented.[5] Even the large number of subjects in the present report is insufficient to exclude completely the possibility of a very weak association between the use of intraoperative TEE and the risk of dysphagia after cardiac surgery.

TABLE I Cardiac Operations During the Period January 1, 1987, Through May 31, 1988

Patient Group	Coronary Revascularization	Valvular Surgery	Coronary Revascularization and Valvular Surgery	Total
Total cardiac operations	955	198	92	1,245
TEE cases	120	59	38	217
Patients with dysphagia	11	7	2	20
Dysphagia with TEE	2	2	0	4
Dysphagia without TEE	9	5	2	16
Dysphagia with TEE	4/217	1.8%	(95% confidence interval 0.5 to 4.6%)	
Dysphagia without TEE	16/1,028	1.6%	(95% confidence interval 0.9 to 2.5%)	
Patients with dysphagia	20/1,245	1.6%	(95% confidence interval 0.5 to 3.1%)	

TEE = transesophageal echocardiography.

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Importance of Technical Variables for Quantitative Measurements by Color Doppler Imaging

Helmut Baumgartner, MD, Heinrich Schima, PhD, and Peter Kühn, MD

Color Doppler imaging provides information on spatial distribution of blood flow and is widely used to evaluate valvular regurgitation and shunt lesions. Estimates of size and shape of flow areas have been suggested to quantify these disorders, particularly in valvular regurgitation,[1,2] where such measurements of jet dimensions are widely used. Although the influence of technical variables—such as ultrasound gain setting and transducer frequency—on color jet areas has been reported,[3–5] this fact is frequently neglected. We studied the magnitude of jet area changes with variation of sample volume size, low-velocity filter, gain setting, sector angle and postprocessing to evaluate their importance for quantitative color Doppler estimates.

We simulated valvular regurgitation in an in vitro pulsatile flow model capable of providing highly reproducible fluid jets. The flow model has been described in more detail elsewhere.[6] *Jets were generated with a pneumatically driven ventricle of an artificial heart, which was passively filled from a reservoir. The ventricle was connected to a cylindrically shaped test chamber (inner length 100 mm, inner width 60 mm). Plates with different orifice diameters were mounted in the center of the chamber's front plane. The outflow of the chamber, radially positioned at the back plane of the cylinder, led back to the reservoir. Flow rates were measured with an electromagnetic flowmeter (Hellige) and pressure gradients across the orifices were measured with fluid-filled catheters and Statham transducers. The test fluid was fresh pooled porcine blood, which was anticoagulated with ethylene diaminetetraacetic acid (2 g/liter).*

Plates with orifice diameters of 1, 2 and 3 mm were used and pressure gradients of 50 and 100 mm Hg were applied. The resulting flow rates ranged from 1.2 to 26.7 ml/s. The ejection time was 700 ms, and the pulse rate was 30 beats/min.

Imaging was performed with a Vingmed CFM 700. The 2.5-MHz mechanical transducer was positioned at the backplane of the test chamber. Pulse repetition frequency was 5.5 kHz. The standard instrument setting was as follows: (1) maximal gain without appearance of artifacts, (2) low-velocity filter 0.25 m/s, (3) sample volume size 2.4 mm, (4) color sector angle 45°, (5) maximal lateral smoothing (postprocessing), (6) variance mode, and (7) frame rate 15/s.

Jet areas were calculated by planimetry (using the on-board quantitation package of the ultrasound device) from frames 300 ms after ejection started (time when the jets had reached their full extension). The measurement was repeated with the standard instrument setting to test the reproducibility. Then, the measurements were repeated after changing the instrument setting as follows: (1) gain was reduced in 12 steps, (2) sample volume size was reduced to 1 mm and to an intermediate position between these 2 settings, (3) lateral smoothing was turned off, (4) low-velocity filter was increased to 0.47 m/s and decreased to 0.19 m/s, and (5) color sector angle was increased to 60°.

A paired t *test was used to test the null hypothesis for the measurements before and after changing the instrument setting.*

Jet areas for the different orifice sizes and pressure gradients ranged from 10.9 to 19.3 cm² and were well reproducible (mean difference 0.2 ± 0.4 cm², all measurements within ±2.5%).

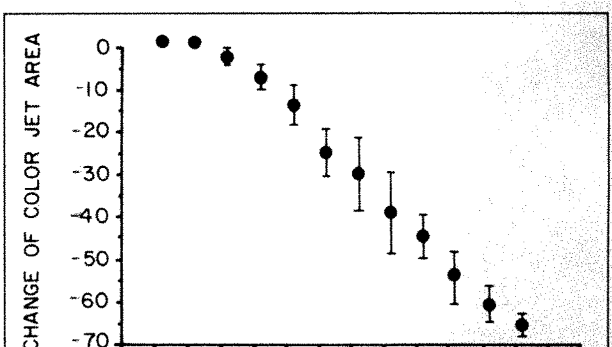

FIGURE 1. Percent change of color jet area with decreasing gain level related to the standard setting—maximal gain without appearance of artifacts (mean ± 1 standard deviation).

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Figure 1 shows the percent reduction of color areas when the gain setting was changed. With a stepwise reduction starting from the maximal gain without appearance of artifacts, only a slight decrease in color area was seen for the first 2 steps, followed by a steep decay with further gain reduction. Figure 2 shows the percent changes of the color areas with variation of the other technical variables (mean ± standard deviation). When the sample volume size was reduced to 1 mm, the color areas decreased by 32.9 ± 4.0% (21.6 ± 7.4% for the intermediate position). The setting without lateral smoothing caused the areas to decrease by 13.6 ± 3.7%. Reduction of low-velocity filter setting to 0.19 m/s was followed by a 12.2 ± 12.5% increase in area, and the elevation to 0.47 m/s by a 32.5 ± 17.3% decrease in area. The magnitude of area change varied substantially for this parameter and was particularly great for the smaller orifices. When increasing the sector angle to 60°, the areas tended to increase slightly, on average (2.5 ± 3.7%), but this was not significant.

The influence of gain setting on color flow images has previously been reported.[3-5] Our results confirm the substantial increase of color jet areas with increasing gain level. At high levels artifacts occur. It has been suggested to set gain at a maximal level without appearance of these artifacts. Our protocol with stepwise gain reduction starting from this level showed that there is some kind of plateau before the areas decrease steeply. This may facilitate a standardized gain setting. However, in clinical studies, individual ultrasound attenuation has to be taken into consideration. This may cause different display of comparable jets in different patients.

Pulse repetition frequency and transducer frequency have also been shown to be important determinants of color flow jet area.[4,5] These parameters are generally known for the used instrument. Our study demonstrates that there are several more physical variables which have not been reported before, and which may cause significant changes in color flow estimates. Sample volume size, low-velocity filtering and postprocessing are independent determinants of color flow jet area. The influence of low-velocity filters is, in addition, highly dependent on orifice size. These technical variables are frequently not reported for Doppler equipment. It can be assumed that they differ for different devices and may contribute to the observed dependence of jet areas on particular equipment used for the measurements.[5]

The results of this study emphasize that instrument settings have to be standardized to obtain reproducible and comparable color flow estimates. As long as generally accepted technical standards are lacking, differences in instrument settings and differences between ultrasound devices may adversely affect the use of uniform color Doppler grading criteria. This has to be considered when previously published grading criteria are used in clinical routine or research studies.

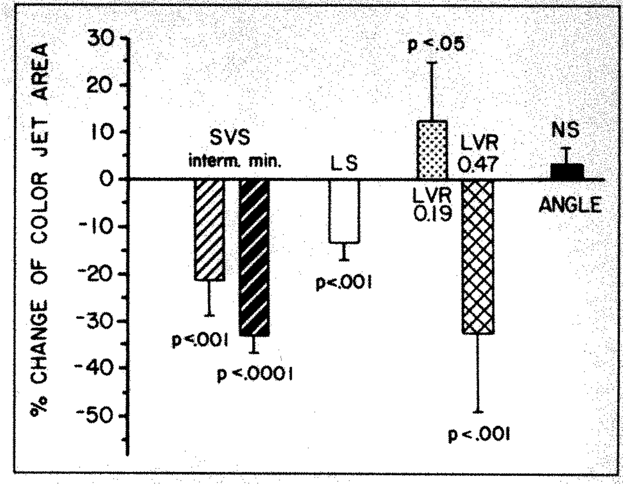

FIGURE 2. Percent change of color jet area after changing technical variables from baseline settings (mean ± 1 standard deviation). interm. = intermediate position; LS = lateral smoothing (postprocessing); LVR = low-velocity rejection (filter level 0.19 and 0.47); min. = minimal SVS (1 mm); NS = not significant; SVS = sample volume size.

Acknowledgment: We thank Gerald Maurer, MD, for helpful discussions during this work.

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Mercury in the Heart

Steven V. Manoukian, MD, and Nanette K. Wenger, MD

Intravenous injection of metallic mercury is well described.[1-5] To our knowledge, echocardiographic findings of intracardiac mercury have not been presented. Sources of intravascular mercury are diverse and include accidental (during blood gas sampling), intentional (believed to increase muscular strength) and suicidal, as in our patient. This article describes certain consequences of intentional intravenous mercury injection, including echocardiographic manifestations.

A 20-year-old black man presented with a 1-week history of dyspnea, cough and a left arm ulcer. Evaluation included left forearm, chest and abdominal x-rays, all of which showed findings consistent with metallic mercury (Figures 1 and 2). He subsequently underwent surgical resection of a segment of the left basilic vein, with confirmation of septic and heavy metal thrombophlebitis with evidence of metallic mercury. It was subsequently determined that approximately 1 week earlier the patient had injected mercury intravenously in a suicide attempt. An echocardiogram showed echo-dense material, consistent with mercury, in the right ventricle and pericardium (Figure 3). Catheter aspiration of the mercury in the right ventricle was attempted through the intravenous route without success. Chelation therapy was begun with oral penicillamine, but the patient failed to return for follow-up evaluation after discharge.

Intravenous injection of mercury, a rare clinical entity, appears to occur most often as a suicide attempt. Alternative sources include accidental injection during blood gas sampling (when used as a sealant in syringes), as well as intentional intramuscular or intravenous administration by athletes to increase muscular strength. The term "quicksilver" may be the origin of the misconception that mercury quickens a boxer's punches.[2]

Sequelae of intravenous mercury injection include local and embolic complications and the syndrome known as mercurialism. Local complications include thrombophlebitis and granuloma formation; local foci should probably be excised so as not to remain as a "reservoir" of mercury for continued slow absorption into the bloodstream. Distant mercury emboli can enter both the right (pulmonic) and left (systemic) circulations. It is speculated that mercury traverses the pulmonic capillary bed, as it has been demonstrated in sites that include the central nervous system, liver, kidney and pericardium.[3]

The echocardiogram is a useful noninvasive means to detect intracardiac and pericardial mercury, as was the case in our patient. The mercury collection was not displaced during supine-to-prone or side-to-side positioning of the patient while continuously recording the echocardiogram. Whether the mercury initially or subsequently interfered with right ventricular outflow and hemodynamics is unknown, but its density is 30 times that of blood. Early during the hospital course, the patient felt most comfortable lying prone and developed chest pain while supine. This may have been due to dense intracavitary mercury in the right ventricle, which subsequently embolized peripherally.

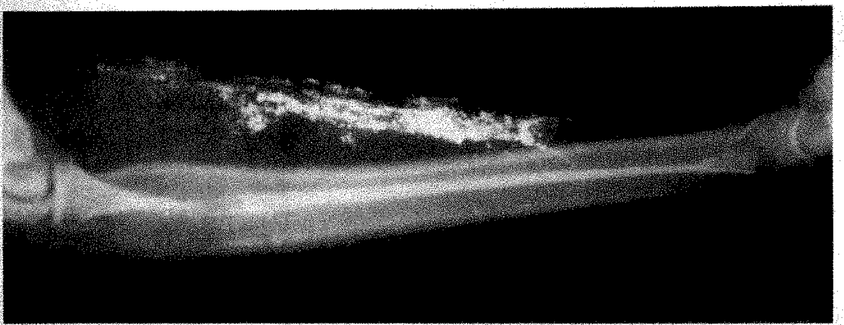

FIGURE 1. Left forearm x-ray. Note the deposits of mercury along the veins of the forearm. (Reproduced with permission from the Department of Radiology, Grady Memorial Hospital.)

Mercurialism has resulted from chronic inhalation of mercurial salts and vapors, but is rarely described as resulting from intravenous administration. The Mad Hatter in *Alice's Adventures in Wonderland* probably demonstrated central nervous system toxicity resulting from inhalation of mercury used in hat manufacturing;

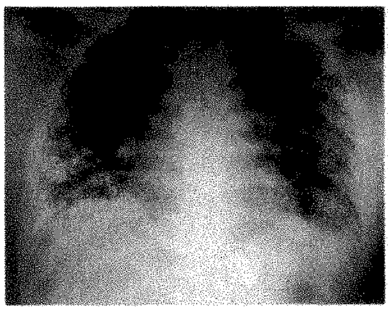

FIGURE 2. Chest x-ray. Note the deposits of mercury in the lung fields and in the cardiac silhouette. (Reproduced with permission from the Department of Radiology, Grady Memorial Hospital.)

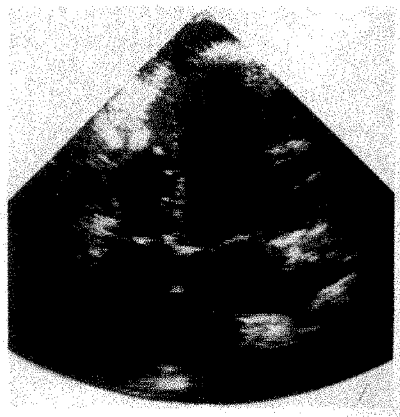

FIGURE 3. Apical 4-chamber echocardiogram demonstrating echo-density consistent with mercury in the regions of the right ventricle and pericardium. (Courtesy of Dr. Joel Felner, Echocardiographic Laboratory, Grady Memorial Hospital.)

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other adverse effects include gastrointestinal (gingivitis, stomatitis, excessive salivation, vomiting, diarrhea) and renal impairment. The toxic effects reflect the slow oxidation of metallic mercury to the soluble mercuric ion, which interacts with protein sulfhydryl groups and interferes with cellular enzyme action. Oxidation of metallic mercury to the toxic ion is slow (in contrast to chronic inhalation); this may account for the rarity with which mercurialism is seen. With time, however, continued absorption occurs, documented by decreasing radiographic evidence of mercury over the years following intravenous injection.[6,7] Intermittent or long-term drug therapy with penicillamine or dimercaprol should therefore be considered.

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Reversible "Cardiomyopathy" After Accidental Adrenaline Overdose

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Cardiotoxic effects of excess catecholamines have been documented since their discovery.[1] We report a case of severe ventricular dysfunction due to inadvertent administration of a large dose of adrenaline with subsequent near complete recovery of ventricular function.

A previously healthy 30-year-old woman was admitted for cone biopsy of the cervix. After intravenous induction, anesthesia was maintained with isoflurane, nitrous oxide and oxygen through a face mask. Cervical injection of what was thought to be 2% lidocaine was undertaken after confirming that the needle was not intravenous. Ventricular premature complexes were immediately noted, followed by bigeminy and sustained ventricular tachycardia. She was given 100% oxygen and lidocaine; the rhythm reverted to sinus tachycardia. Pulmonary edema rapidly ensued requiring intubation. It was subsequently noted that the drug injected was 1:1,000 epinephrine, to a total dose of 7 mg. Blood pressure decreased to 80 to 120 mm Hg systolic after a peak of 152/110 mm Hg. Over the following 4 to 6 hours, hypotension progressed and she was treated with intravenous saline solution and dopamine. A pulmonary artery catheter was inserted; the initial cardiac index was 1.8 liters/min/m^2, and systemic vascular resistance 2,100 dynes·s·cm^{-5}. Nitroprusside was temporarily added. The electrocardiogram showed sinus tachycardia, incomplete right bundle branch block and left anterior hemiblock. Echocardiography showed severe global left ventricular dysfunction with normal ventricular size. Moderate hypokinesia of the right ventricle was seen. The patient became increasingly hypotensive with arterial blood pressures as low as 55/25 mm Hg; nitroprusside was withdrawn, while noradrenaline and phentolamine infusions and intraaortic balloon pump support were instituted. On this regimen her systemic vascular resistance stabilized at 1,100 to 1,500 dynes·s·cm^{-5} with a cardiac index of 1.9 to 2.8 liters/min/m^2. Mild metabolic acidosis was seen within the first 24 hours with 17 mmol of bicarbonate and creatine kinase increased to 615 U/liter (normal <125 U/liter) at 24 hours with a positive MB band. On the second and third hospital days, hypotension and tachycardia continued. By the fourth hospital day her condition had stabilized, with a systemic vascular resistance of 1,000 dynes·s·cm^{-5}, blood pressure of 75/52 mm Hg and cardiac index of 2.6 liters/min/m^2, and noradrenaline and phentolamine infusions were withdrawn. Sedation and paralysis were withdrawn on day 5 and a repeat echocardiogram revealed slight improvement in left ventricular function, mild hypokinesia of the right ventricle and normal

TABLE I Adrenaline Overdose—Cardiovascular Status and Hemodynamic Support

DAY	HR	BP	SVR	CI	IABP	DA	NA	P	EF (%)
1	130	78/44	2,100	1.8	0	+	0	0	<20
1	140	78/58	1,300	2.4	+	+	0	+	<20
2	125	78/60	1,400	2.1	+	+	+	+	
3	120	84/56	1,200	2.5	+	+	+	+	
4	105	76/52	1,000	2.7	+	+	0	0	
5	100	84/46	1,000	3.1	+	+	0	0	20–39
6	89	104/54	900	3.4	0	0	0	0	
7	98	110/64	750	4.6	0	0	0	0	
8	80	112/66	—	—	0	0	0	0	40–59

All values are average for 24 hours.

BP = blood pressure (mm Hg); CI = cardiac index (liters/min/m^2); DA = dopamine; EF = ejection fraction (echocardiogram); HR = heart rate (beats/min); IABP = intraaortic balloon pump; NA = noradrenaline; P = phentolamine; SVR = systemic vascular resistance (dynes·s·cm^{-5}).

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left ventricular size. On day 6 the intraaortic balloon pump and dopamine were withdrawn and she was extubated. A repeat echocardiogram on day 10 showed that global left ventricular function had improved to normal. A blood pool scan performed at rest before discharge on day 23 showed an ejection fraction of 49%. She is asymptomatic 1 year later. Table I summarizes the cardiovascular status and hemodynamic support used during the first 9 days in the hospital.

Catecholamines are known to cause a wide spectrum of cardiotoxicity.[1] Animal studies have shown myocardial depressant effects of an oxidant product of epinephrine, which causes dose and time-dependent irreversible mitochondrial and myocardial damage.[2] Dysfunction is initially functional because of adrenergic receptor-mediated calcium influx, which may cause myocardial injury alone or in concert with coronary vasoconstriction. Endogenous overproduction of catecholamines can cause cardiac abnormalities in patients with pheochromocytoma, a cardiomyopathy, and histologic abnormalities have been documented. This dysfunction is reversible with medical or surgical management of the underlying tumor.[3] Patients with subarachnoid hemorrhage develop focal or diffuse left ventricular dysfunction,[4] presumably related to the massive sympathetic discharge associated with brain injury, because the dysfunction is attenuated by α and β blockade[5] and surgical sympathectomy.[6] These abnormalities are also transient in nature with complete recovery documented.[4] This report is the first recorded case of the nearly fatal consequences of inadvertent administration of a very large dose of epinephrine, with the subsequent development of a severe catecholamine-induced "cardiomyopathy." Paradoxically, after the initial phase of massive catecholamine excess, this patient required exogenous catecholamines to support the injured, dysfunctional myocardium and maintain adequate perfusion pressure to vital organs. This case illustrates the need for aggressive support of patients receiving overdoses of catecholamines, with the expectation that, while cardiac function may be extremely impaired early in the course of the illness, recovery is virtually complete over time.

Addendum: Since preparation of this manuscript for publication, we have treated a similar case of a 21-year-old woman who received 3 mg of adrenaline intravenously for the treatment of anaphylaxis. Myocardial dysfunction persisted for 36 hours before resolving completely.

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Persistent Left Fifth Aortic Arch with Complex Coarctation

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Persistent fifth aortic arch is a rare anomaly, with only 22 cases reported.[1,2] Its recognition and successful management when associated with coarctation is even rarer. We present a child with persistent left fifth aortic arch and complex coarctation successfully diagnosed and repaired.

A 6-year-old girl was referred for evaluation of pseudocoarctation of the aorta. At 2 years old, she was noted to have an innocent murmur and normal pulses in the legs and arms. An electrocardiogram showed findings of Wolf-Parkinson-White syndrome. At 3.5 years, echocardiography showed normal intracardiac structure and "buckling" of the aorta. At 4.5 years, a discrepancy was noted between the upper and lower extremity pulses. A magnetic resonance imaging study was interpreted as showing tortuosity and elongation of the aortic arch between C7 and T1 and narrowing of the descending portion of the thoracic aorta at T4.

At presentation, she was asymptomatic. Blood pressure was 122/76 mm Hg in the right arm, 110/88 mm Hg in the left arm and 90/60 mm Hg in the left leg. Pulses were normal in the right arm, but diminished in the left arm and lower extremities. Heart sounds were normal. An ejection sound and 2/6 systolic ejection murmur were heard at the right upper sternal border. Echocardiography showed a bicommissural aortic valve without significant stenosis or insufficiency and a coarctation of the aorta. There was aneurysmal dilatation of the left subclavian artery. Cardiac catheterization showed a 15-mm Hg pressure difference between the ascending and descending aorta. Ascending aortic angiography showed a competent, bicommissural aortic valve and a normal ascending aorta that gave rise to 2 anterior, left-sided transverse arches. The fourth aortic arch gave rise to an innominate, left carotid and dilated left subclavian artery. The fourth arch joined the descending aorta at the junction of the more caudal fifth aortic arch and the descending aorta. Coarctations of the aorta were noted just distal to the junction of the

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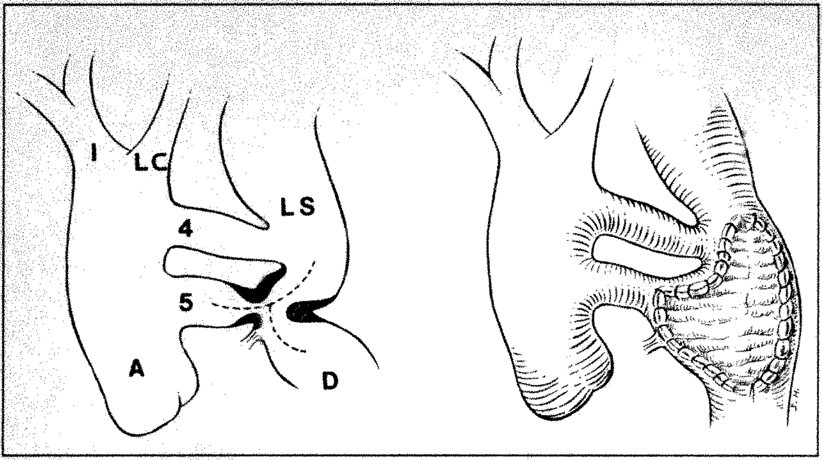

FIGURE 1. *Left,* schematic drawing of persistent left fifth aortic arch (5) with coarctations *(shaded areas)* of the fourth and fifth arches. *Right,* coarctation repair of persistent fourth and fifth arches. Y-shaped incision from the descending aorta (D) through the coarctations into the fourth and fifth aortic arches. Knitted Dacron™ patch onlay to augment diameter of hypoplastic vessels and preserve both aortic arches is seen. A = ascending aorta; I = innominate artery; LC = left carotid artery; LS = left subclavian artery; 4 = embryologic fourth arch remnant.

fourth aortic arch and the left subclavian artery and at the junction of the fifth aortic arch and the descending aorta. The anatomy was confirmed at surgery. The ductus arteriosus ligament was just distal to the junction of the fifth aortic arch and the descending aorta. A Y-shaped incision was made from the descending aorta across the coarctation sites (Figure 1). A patch aortoplasty repair was completed, augmenting both the fourth and fifth aortic arches. Arterial pulses and blood pressures were normal in the arms and legs postoperatively and on follow-up.

Persistence of the fifth aortic arch is a rare congenital defect. Although normally only transient, the presence of a fifth aortic arch in human embryos was described by Congdon.[3] Persistence of a fifth aortic arch has 2 patterns, with distal connections to either the dorsal aorta or the pulmonary artery, and may present as either systemic to systemic or as systemic to pulmonary connection.[4]

Persistent fifth aortic arch may be associated with congenital heart diseases, including cor triatriatum, patent ductus arteriosus, tricuspid or pulmonary atresia, or both, ventricular septal defect, transposition of the great arteries, interrupted aortic arch and coarctation of the aorta. Coarctation was noted in 6 of 21 patients with persistent fifth aortic arch.[1] Konishi et al[5] reported a case of persistent left fifth aortic arch with coarctation of the aorta distal to the junction of a dilated left subclavian artery and left fifth aortic arch. Their repair included placement of Gortex™ tube grafts. Others have repaired coarctation of a persistent fifth aortic arch by ligation of the persistent arch.[6] This patient's repair had the benefit of not sacrificing a great artery and not using tube grafts.

Echocardiography is the procedure of choice for assessment of coarctation of the aorta. The dilatation of the subclavian artery could not be explained and catheterization was performed. The imaging sections of the magnetic resonance imaging study performed at the referring hospital were too wide to show the persistent fifth aortic arch and double coarctation. Cardiac catheterization correctly identified the arch anatomy, allowing proper counseling of the family and preparation of a surgical plan.

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Tricuspid Valve Honk Due to Pulmonary Hypertension Secondary to Left Atrial Myxoma

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A tricuspid "honk" is a rare and fascinating auscultatory phenomenon that has been heard in patients with congestive cardiomyopathy,[1] a right-sided cardiac pacemaker catheter,[2] tricuspid valve prolapse,[3] cor pulmonale[4] and mitral stenosis with pulmonary hypertension.[5] We report a patient in whom a tricuspid honk was due to a left atrial myxoma causing severe pulmonary hypertension and secondary tricuspid regurgitation.

A 38-year-old woman presented December 1, 1989, with increasing dyspnea on exertion for 1 month and pedal edema for 3 days. A thrill was palpated only on inspiration along the right sternal border; a loud S_1 and a split S_2 with an accentuated pulmonic closure sound was present. A grade 2/6 holosystolic, high-frequency murmur was heard at the lower right sternal border, which became much louder, honking in early systole during inspiration (Figure 1). An echocardiogram demonstrated a 6.5 × 3.8 cm left atrial mass that almost completely filled the left atrium and protruded into the mitral valve during diastole (Figure 2). The right atrium and right ventricle were dilated. At operation, a large left atrial myxoma was removed. Before removal, the pulmonary artery pressure was 107/55 mm Hg. Five hours later, pulmonary artery pressure was 62/31 mm Hg and the honk could no longer be heard. A repeat echocardiogram did not demonstrate any tricuspid regurgitation.

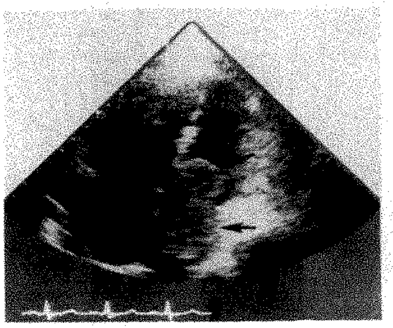

FIGURE 2. Echocardiogram of apical 4-chamber view demonstrating large left atrial myxoma *(arrows)* almost filling the left atrium and protruding through the mitral valve. The right heart is very dilated.

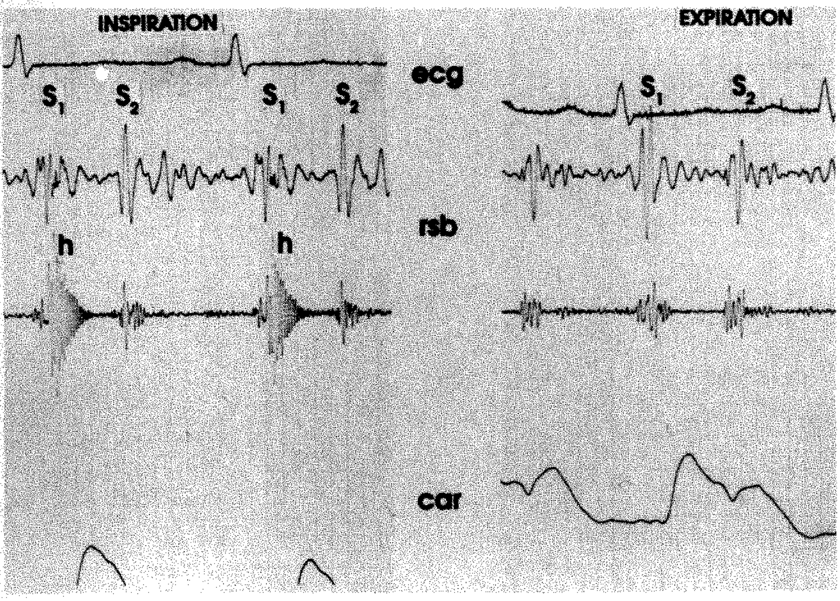

FIGURE 1. Phonocardiogram on inspiration and expiration illustrating tricuspid honk (h) on inspiration only. With inspiration the carotid pulse (car) was displaced almost off the recording. ecg = electrocardiogram; rsb = right sternal border.

This case adds another cause for a tricuspid honk and a new auscultatory finding for a left atrial myxoma.[6] Removal of the myxoma allowed resolution of the marked pulmonary hypertension and, presumably, normal coaptation of the tricuspid valve.

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Atrial Natriuretic Peptide and Chronic Constrictive Pericardial Heart Disease

The article by Svanegaard et al[1] is a superb contribution to the understanding of atrial natriuretic peptide (ANP), because the authors took unique advantage of the exclusion from pericardial constriction of their patient's left atrium. They cited our original contribution on ANP during pericardiectomy for constriction,[2] but it is necessary to point out that our patient differed significantly from theirs: Our patient had chronic constriction, which was missed for 8 years before she was referred for consultation, and she also had the classic form of general constriction involving all chambers; their patient conformed to one of several anatomic models of *local constriction*.[3] Their protocol was ingenious and they have advanced our knowledge considerably. I would be grateful if the authors would clarify some points that may have been more obvious before the usual drastic manuscript shortening when converting an article to a Case Report.

On page 119 the authors write that atrial pressure and transmural pressure are "...not the main stimulus for ANP production."[1] But on page 120, they agree with most investigators that "...stretch, not pressure, is the major stimulus...." since this is indeed the conclusion reached from repeated experiences with cardiac tamponade and recently with typical (i.e., generalized) constriction.[2,4] Yet how do the authors separate stretch from transmural pressure? After all, cardiac chambers do not stretch abnormally unless there is increased transmural pressure. Another name for transmural pressure is "chamber distending pressure"; stretch and distention are equivalent.

An additional implication of our report[2] and, in some respects, theirs,[1] is that significant constrictive scarring acts comparably to significant tamponading fluid, in that transmural pressure is critically reduced or eliminated despite the existence of pleural pressure—comparable to normal pericardial pressure—across the thick wall formed by the heart plus constricting pericardium. In cardiac tamponade, where average ventricular diastolic and intrapericardial pressures become equilibrated, one assumes no effective average transmural pressure, whereas before their investigation[1] and ours,[2] one might have assumed that pleural pressure in constriction might have had some effect similar to normal pericardial pressure. That effective transmural pressure only existed in the authors' patient's left atrium[1] meant that the adherent, constricting pericardium on their patient's other 3 chambers, as in all of our patient's chambers,[2] cancelled or buffered any effective transmural pressure.

Finally, the hypothesis about ANP and its possible causative role in pulmonary edema was pointed out previously.[3] They list that report as reference 6, but curiously do not cite it in the text. [*Editor's note: Reference 6 was cited in the authors' original manuscript, but due to a typographical error appeared as a second citation of reference 5. See page 120, column 2, paragraph 2, line 10.*[1]] Nonetheless, the authors' brilliant exploitation of the unusual anatomic distribution of the constricting lesion indirectly supports this hypothesis. While the right atrium is much less likely to escape constriction,[3] such an unlikely event should be equally exploitable.

These remarks are made to seek clarifications rather than to criticize adversely an excellent and extremely valuable report.

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23 July 1990

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REPLY: We agree that stretch and distension are equivalent and that this is the main stimulus for ANP. The question is whether stretch and transmural pressure are equivalent. It is correct that cardiac chambers do not stretch abnormally unless there is an increased transmural pressure. In constrictive pericardial disease, stretch is not possible because of the compression against the calcified pericardium. In the restricted areas of the heart, we have considered the pleural pressure to be equal to intrapericardial pressure and the pleural pressure is believed to be equal before and after operation. The transmural atrial pressure is in this way determined by the average atrial pressure, which was found to be increased before operation (and increased further during exercise). When the calcified pericardium is removed by operation, the decompression makes the transmural pressure decrease. As pointed out in your report (reference 2 of your letter, page 1324) transmural pressure is expected to decrease after pericardiectomy, but as ANP is increasing, when stretch is possible after operation, as in your congested patient, the stretch and not transmural pressure most likely is the stimulus for ANP production.

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4 September 1990

Ejection Fraction and Induced Sustained Ventricular Tachycardia

In a retrospective study from the Philadelphia Arrhythmia Group[1] on patients with spontaneous nonsustained ventricular tachycardia (VT) after myocardial infarction, the authors concluded that "left ventricular function had only minimal effect on the result of electrophysiologic testing." This statement may not have been adequately supported by the investigators' data. The following limitations of the study could be cited: (1) Left ventricular ejection fraction was not determined in 17% of the study patients, who were assigned to groups with no, mild or severe impairment of left ventricular function only on the basis of New York Heart Association classification. (2) The time interval between evaluation of left ventricular function and programmed ventricular stimulation was not specified. (3) Statistical analysis may not have been carefully performed. Based on Figure 1, sustained monomorphic VT was induced in 8 of 47 patients (17%) with preserved left ventricular function (ejection fraction $>50\%$ or New York Heart Association class I) versus 40 of 88 patients (45%) with severely impaired left ventricular function (ejection fraction $<35\%$ or New York Heart Association class III or IV). This difference is highly significant by chi-square test with Yates' correction for continuity (chi-square = 9.6, $p < 0.002$).

Thus, the study from the Philadelphia Arrhythmia Group is concordant with previous investigations in showing that ejection fraction is an important determinant for the induction of sustained VT.[2-4] A prospective study from our laboratory[5] on 105 patients with spontaneous nonsustained VT found that ejection fraction was an independent predictor of the outcome of programmed stimulation. In this study, sustained monomorphic VT was induced in 19 of 49 cases with ejection fraction $<40\%$ and in only 3 of 56 cases with ejection fraction $\geq 40\%$ (39 versus 5%, $p < 0.0001$).

We agree with the authors who feel that the prognostic role of ejection fraction studies and programmed stimulation in patients with spontaneous nonsustained VT requires further assessment. There is strong evidence that ejection fraction studies, together with the signal-averaged electrocardiogram, may be used for stratification of these patients into groups at high or low risk for induced tachyarrhyth-

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mias. The probability of inducing sustained VT is significantly higher in the presence of low ejection fraction, late potentials, or both, on the signal-averaged electrocardiogram.[3,5-7] Finally, there is also evidence that patients with no late potentials and no inducible sustained VT and with ejection fraction >40% may be followed safely off antiarrhythmic drugs, with a low risk of sudden cardiac death.[7]

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Nabil El-Sherif, MD
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6 April 1990

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REPLY: Drs. Turitto and El-Sherif cite "limitations of the study." The fact that 17% of the patients did not have direct measurement of left ventricular function is unlikely to have impacted on a study of 205 patients, especially when a functional assessment was available. We would refer Turitto and El-Sherif to a sentence that they may have missed in the results section: ". . . the results remained unaltered when we analyzed data only for patients in whom left ventricular function was quantified by ejection fraction measurement."[1] Because the study was retrospective, we have no way of knowing the exact time lag between measurement of left ventricular ejection fraction and programmed ventricular stimulation, but we have no reason to suspect that there was an inordinate delay between the 2 tests. Nearly all of the patients had both studies during the same hospitalization. Because at least 1 month had elapsed between the infarction and study, we doubt that the arrhythmic substrate was in a state of flux.

We believe that Turitto and El-Sherif may have overinterpreted our conclusion regarding the impact of left ventricular function on the results of electrophysiologic testing. It is obvious that more patients with poor left ventricular function are inducible to sustained monomorphic VT than those with well preserved ejection fractions. That observation has been made by a variety of investigators including ourselves.[2] This finding is relatively meaningless without some information regarding the prognostic value of inducibility. The crux of the question is whether the results of programmed stimulation can be used either to ferret out the individual at risk or to select therapy. The articles referenced by Turitto and El-Sherif do not provide conclusive evidence in this regard. The papers by Furukawa,[3] Buxton,[4] Turitto[5] and their co-workers deal only with the issue of inducibility and do not address the question of long-term prognosis. Gomes et al[6] did attempt to follow patients but treated inducible patients with drugs selected in the electrophysiology laboratory and also treated a substantial percentage of noninducible patients with "prophylactic antiarrhythmic therapy." Turitto's most recent study[7] reported a 34% cardiac mortality in inducible patients that apparently was not statistically different from a 19% mortality in patients without inducible sustained VT/fibrillation. None of these studies have the statistical power or homogeneity of ours, in which nearly half of the patients who experienced VT or a cardiac death during the follow-up period had been noninducible in the electrophysiology laboratory. Whether or not signal-averaging can improve the chances of predicting an event-free follow-up in these patients remains to be seen but admittedly appears promising.[8]

The decision to leave low-risk individuals untreated and to treat inducible patients aggressively is based on conflicting information, all of which is contaminated by the fact that patients enrolled in trials to date have been treated with antiarrhythmic drugs in the follow-up period, treatment that may have been responsible for a worse outcome in the more impaired patients. Inducing sustained VT in asymptomatic patients may open a Pandora's box that the unwary physician may wish had never been unlocked. Until a prospective study is completed in which high-risk patients are studied and followed without antiarrhythmic drug therapy, we would not encourage physicians to carry out programmed stimulation in patients with asymptomatic nonsustained VT, except for the purposes of data collection in well-conceived clinical trials.

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Harvey L. Waxman, MD
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15 May 1990

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Quadricuspid Aortic Valve

We recently read the recent article by Feldman et al[1] describing their echocardiographic experience with quadricuspid aortic valves. It was of interest to note the great similarities in the diagnosis and occurrence of quadricuspid aortic valves diagnosed by 2-dimensional echocardiography and that of large autopsy series.[2] While the occurrence of quadricuspid aortic valves is rare, it may well be seen by physicians working in busy echocardiographic laboratories.

The embryology of this rare occurrence is of interest and is as follows. The semilunar valves are derived from mesenchymal swellings in the aortic and pulmonary trunks after the truncus arteriosus has been partitioned (by the fourth week of gestation). Normally, 3 outgrowths bulge into the lumen of each great vessel and develop into 3 semilunar cusps that coapt in the center of the valve orifice. It has been suggested that an abnormal number of cusps result from developmental changes in the early stages of truncal separation. The outcome is either a dyssymmetry in the number of primordial valve cusps or abnormal proliferation or fusion of these mesenchymal buds, resulting in 4 subendothelial buds appearing in either the aortic or pulmonary trunk.[3] A true 4-cuspid valve has corpus arantii on each cusp, indicating that the valve resulted from abnormal embryogenesis; a pseudo-quadricuspid valve is secondary to bacterial endocarditis or rheumatic valvulitis.

We applaud the authors of this fine report for their time and dedication in the review of almost 100,000 echocardiographic studies to provide the data described in their article.

Shale Gordon, MD
Michael Butler, CVT
Bellflower, California
25 April 1990

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Endomyocardial Biopsy in Cardiac Transplant Recipients Using the Femoral Venous Approach

I read with interest the article by Goy et al[1] on right ventricular endomyocardial biopsy in cardiac transplant recipients. Several points deserve comment. The femoral vein technique of myocardial biopsy is now commonplace in all centers that do a fair number of transplants and endomyocardial biopsies. The technique is well described[1] but misleading. Specifically, confirmation of the position of the bioptome against the ventricular septum is important. In my experience with the transfemoral myocardial biopsy technique in >500 patients, 2 cardiac perforations have occurred (with tamponade), both in patients with dilated cardiomyopathy. No complications of this nature were identified in our subset of transplant recipients (>90 patients with >3 biopsy procedures per patient). In addition, we caution operators to open the biopsy jaws within the sheath before exiting it, to insure that the open jaws contact the myocardium and to avoid perforation by the rounded closed jaws. Our colleagues on the transplant service appreciate measurement of right ventricular and right atrial pressures through the side arm of the long sheath, although Goy et al do not believe this is necessary.

No biopsy procedure had to be repeated due to insufficient sampling by Goy et al. We have found myocardial tissue of transplant patients "denser" (i.e., more difficult to biopsy) than that of myocarditis or idiopathic dilated cardiomyopathy patients. In their 16 patients, they apparently did not encounter fibrotic tissue, which occasionally occurs in patients who undergo multiple biopsy samplings. If more of their patients had been followed for several years, it is likely that some samples might have indicated fibrosis from repeated biopsy sites and/or sufficient material. I agree that transfemoral myocardial biopsy is a safe and common practice, but, unlike Goy et al, I advocate cautious catheter placement to avoid biopsying the right ventricular free wall or apex, the thinnest portion of the heart.

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30 April 1990

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Vasomotor Properties of Internal Mammary Arteries, Saphenous Vein Bypass Grafts and Native Coronary Arteries

The results of the study by Hanet et al[1] were identical to those recently reported by Kitamura et al.[2] In each of the 10 patients studied by Hanet et al after coronary artery bypass surgery, the left internal mammary artery graft was used with concomitant saphenous vein grafts. I wonder if Hanet et al compared the internal mammary artery grafts with the saphenous vein grafts with regard to their responses to ergometrine and isosorbide dinitrate. Such a comparison would not only be interesting but have important clinical implications. If saphenous vein bypass grafts behave more like the native coronary arteries in their responses to ergometrine and isosorbide dinitrate, then the internal mammary artery will be the conduit of choice for bypassing not only coronary arteries with fixed obstructions but also coronary arteries that develop spasm in variant angina or in the "variant of the variant."[3]

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3 May 1990

1. Hanet C, Wijns W, Decoster P, Pouleur H, Dion R, Rousseau MF. Angiographic evaluation of vasomotor properties of internal mammary arteries before and after coronary artery bypass grafting in men. *Am J Cardiol* 1990;65:918–921.
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REPLY: We did not compare the responses of internal mammary artery and saphenous vein grafts to ergometrine and isosorbide dinitrate in the same group of patients. This would have required insertion of 2 catheters for simultaneous catheterization of arterial and venous grafts and multiple displacements of the x-ray table between contrast injections that may have affected the reproducibility of angiographic measurements. However, preliminary data on the response of saphenous vein grafts to ergometrine and isosorbide dinitrate had been obtained with a similar study protocol in 4 patients. Changes in lumen diameter were inconsistent after ergometrine (3.37 ± 0.70 to 3.37 ± 0.66 mm) and only a slight vasodilation was observed in 3 patients after isosorbide dinitrate (mean, 3.44 ± 0.69 mm). The mean difference between minimal and maximal lumen diameters appeared to be smaller for saphenous vein grafts (0.11 ± 0.04 mm) than for mammary artery grafts (0.25 ± 0.14 mm),[1] suggesting that quantitative differences in responsiveness to pharmacologic interventions exist between both types of grafts. This phenomenon could result from differences in endothelial function but also from structural differences between internal mammary arteries and segments of saphenous veins transferred into the arterial circulation.

If the vasomotor properties of internal mammary arteries could have some physiologic implications in regulating myocardial blood flow after surgery, extrapolation of these data to the surgical treatment of variant angina may be hazardous. Although rare, spontaneous spasms of both saphenous vein[2] and internal mammary artery grafts[3,4] several months after bypass surgery have been reported; the absence of vasospastic response to ergometrine in our patients (none of whom had variant angina) does not preclude the existence of a local hypersensitivity to this or to other stimuli in some cases.

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31 May 1990

1. Hanet C, Wijns W, Decoster P, Pouleur H, Dion R, Rousseau MF. Angiographic evaluation of vasomotor properties of internal mammary arteries before and after coronary artery bypass grafting in men. *Am J Cardiol* 1990;65:918–921.
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Comparison of Proximal Left Anterior Descending and Circumflex Coronary Artery Dimensions in Aortic Valve Stenosis and Hypertrophic Cardiomyopathy

Whereas coronary vasodilator reserve has been used to assess the hemodynamic consequence of epicardial coronary artery stenoses[1,2] and microvascular flow,[3] little attention has been focused on the adequacy of the size of epicardial arteries per se. Kimball et al[4] suggest that absolute coronary dimension may be important. While these authors apparently did not take into account the exponential relation between diameter and flow, they raise some interesting questions.

To evaluate the issue of epicardial flow by a mathematical model, flow (Q) through the left anterior descending artery (LAD) can be calculated using Hogen's modification of Poiseuille's law:

$$Q = \frac{\pi(Pi - Po)r^4}{8\ nl}$$

The LAD is assumed to be of constant radius (2 mm), 4 cm in length[1] and nonbranching. A pressure head (Pi − Po) of 75 mm Hg is assumed using a mean aortic pressure of 80 mm Hg minus a mean right atrial pressure of 5 mm Hg. Basal blood viscosity (n) is 2.7 dynes s/cm^2 and a converting factor of 10^5 dynes cm^{-2}/7.5 cm Hg is needed. The equation now reads:

$$Q = \frac{3.14\ (7.5\text{ cm Hg})(10^5\text{ dynes cm}^{-2}/7.5\text{ cm Hg})(0.2\text{ cm})^4}{8\ (2.7\text{ dynes s cm}^{-2}(4\text{ cm})}$$

This calculates to a potential maximum flow of 5.81 ml blood/s or 349 ml/min through the LAD. Mean resting LAD (or great cardiac vein) flow has been measured to be 70 ml/min.[3,5] Using the ratio of maximum to basal flow, the coronary flow reserve would be fivefold, which closely approximates the findings during dipyridamole- or hyperemia-induced vasodilatation in man.[1] However, if a 3-mm diameter LAD were supplying the same vascular bed, the potential maximum flow would be 1.84 ml/s or 110 ml/min and the flow reserve would decrease abruptly to only 1.6. Thus, a 25% smaller radius would be associated with a 68% reduction in flow reserve.

Despite the multiple assumptions that have been made, this mathematical model closely mimics physiologic conditions. Whereas the concept of flow limitation by vessel size has been well recognized in hypertrophy, wherein the mass of muscle may outstrip supply,[3] the normal physiologic relation between vessel caliper and area of supply may need reassessment. The epicardial arteries may determine maximal flows and therefore be the limiting factor for flow reserve in the absence of significant epicardial stenoses or microvascular abnormalities. Arboration of the arterial tree should lead to an increasing total cross-sectional area; therefore, the microvasculature should not be the physiologic limit to maximum flow. Is it possible that some patients with relatively small but "normal" epicardial coronary arteries outstrip supply during exercise? Would such patients show increased susceptibility to vasomotor modulations? Is this similar to skeletal muscle pain on exertion? Is this yet another etiology of anginal chest pain with normal coronary arteries? The findings of Kimball et al[3] suggest that these questions need to be asked and answered.

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Kenneth M. Kessler, MD
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17 May 1990

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Intravenous Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm

I read the article by Noc et al[1] in which they point out the lack of studies where amiodarone is used to terminate atrial fibrillation. I call the attention of the authors and readers to two other publications on this subject. Faniel and Schoenfeld[2] gave intravenous amiodarone to 26 consecutive patients with atrial fibrillation and rapid ventricular response. An 80% conversion to sinus rhythm was seen within 24 hours, with a mean conversion time of 177 minutes. We[2,3] also gave intravenous amiodarone to 26 patients with paroxysmal or new atrial fibrillation: 12 patients (46%) reverted to sinus rhythm within the first 30 minutes (mean 14 ± 9); 1 converted to atrial flutter within 10 minutes and to sinus rhythm 40 minutes later. An additional 6 patients (23%) converted to sinus rhythm after 2 to 8 hours, whereas 7 patients (27%) required other medications or modalities of therapy to restore sinus rhythm. Amiodarone was also effective in slowing the ventricular response from 143 ± 27 to 96 ± 10 beats/min. We agree with Noc et al that amiodarone is far superior to verapamil (and to digoxin) in converting atrial fibrillation to sinus rhythm.

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18 May 1990

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Do Multiple Short Bouts of Exercise Really Produce the Same Benefits as Single Long Bouts?

In a recent article by DeBusk et al,[1] it was concluded that multiple short bouts of moderate-intensity exercise (three 10-minute bouts/day) increased peak oxygen uptake significantly and were as effective as single long bouts of moderate-intensity exercise (one 30-minute bout/day) in producing training effects. We wish to address several problems with the methodology and overstated conclusions of this study.

First, it must be emphasized that the authors only measured functional capacity as assessed by VO_2 max and submaximal exercise parameters. An increase in functional capacity is but one potential benefit of aerobic exercise.

Second, entry criteria allowed some subjects to have been exercising by jogging 38 minutes/week (19 minutes twice/week) or by walking 120 minutes/week (60 minutes twice/week). This amount of exercise in some subjects would have been almost as much as they did during the 8-week experimental period. If they exercised at 70 and 71% of their peak heart rate, this would have been the equivalent of about 54 to 56% of VO_2 max. If the above is true, and subject log records seem to verify this fact, then these subjects could not have been jogging. The mean pre-VO_2 max was 33.3 in the long-bout group and 32.1 in the short-bout group. Fifty-five percent of 33 ml/kg/min is 18.2 ml/kg or 5.2 METs. The American College of Sports Medicine equation for energy cost of running at 5.0 mph on a level ground predicts 8.6 METs or 91% of these subjects' VO_2 max.[2]

Third, and most important, the group that trained for 30 minutes continuously each session increased its maximal oxygen uptake by 14% (VO_2 max increase from 33.3 to 37.9 ml/kg/min). This is twice the increase experienced by the short-bout group, which trained for 10 minutes 3 times/day. The short-bout group demonstrated a 7.5% increase (VO_2 max increased from 32.1 to 34.5 ml/kg/min). In addition, a change of 2.4 ml/kg/min (7.5%) is hardly outside the range of measurement error for computer-based indirect calorimetry and biologic variability.[3,4]

Therefore, it is difficult to accept the conclusion that "multiple short bouts of moderate-intensity physical exercise produce significant training effects." It does the population a disservice to suggest that the same benefits can be derived from multiple short bouts of exercise, when, in fact, the results demonstrate a "practically" unimportant (though "statistically" significant) change in maximal oxygen uptake. The multiple short-bout exercisers experienced only little more than half (57%) the increased peak oxygen uptake experienced by the long-bout exercisers. This study does not even address the likely ineffectiveness of multiple 10-minute bouts/day of exercise on improving coronary risk factors. Finally, I would contend that many persons would find it more impractical to change into exercise clothes 3 times per day. In fact, the total time devoted to exercising per day would be greater when performed in this manner. While it is important to encourage all sedentary individuals to "move about," it is equally important to indicate to the populace that there is an essential and an optimal amount of exercise or physical activity that is necessary for deriving the most return for the time invested. DeBusk et al did not convince us that multiple short-bout exercise is a viable alternative to single long-bout sessions. It is our opinion that a more appropriate conclusion based on the results of this study would have been: although 3 repeated 10-minute bouts of aerobic exercise per day produced a modest increase, sustained, continuous 30-minute bouts resulted in a significantly greater increase (43%) in VO_2 max. Therefore, continuous 30-minute bouts of aerobic exercise, performed 5 days/week (ironically, about 1,500 to 2,000 kilocalories/week) are preferred over three 10-minute bouts.

Tom LaFontaine, PhD
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15 June 1990

1. DeBusk RF, Stenestrand U, Sheehan M, Haskell WL. Training effects of long versus short bouts of exercise in healthy subjects. *Am J Cardiol* 1990;65:1010–1013.
2. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. Philadelphia: Lea and Febiger, 1986:171, Table D-3.
3. Kannagi T, Bruce RA, Hossack KF, Chang K, Kusumi F, Trimbel S. An evaluation of the Beckman metabolic cart for measuring ventilation and aerobic requirements during exercise. *J Cardiac Rehab* 1983;3:38–53.
4. Katch V, Sady S, Freedson P. Biological variability in maximum aerobic power. *Med Sci Sports Exerc* 1982;14:21–25.

REPLY: LaFontaine and Robbins state that we measured functional capacity only in relation to increased VO_2 max and decreased submaximal heart rate. In fact, we also measured treadmill exercise time, a measure of increased endurance, and found a comparable (12%) increase in subjects completing long and short bouts of exercise. Heart rate at submaximal exercise also decreased to a comparable extent (6%) in both groups. Only VO_2 max was significantly different between the 2 groups, i.e., a 7.6% increase in the short bouts versus 13.9% in the long bouts.

While LaFontaine and Robbins are technically correct in stating that subjects could have been performing substantial amounts of exercise before participation in the study, few subjects were as active as they suggest. Randomization would account for the allocation of such active subjects to the 2 groups. In any event, inclusion of such subjects would have increased the difficulty of demonstrating an increase in functional capacity with either exercise regimen.

LaFontaine and Robbins question whether a 7.6% increase in VO_2 max in the short-bout group is clinically meaningful. An increase in treadmill duration and decrease in submaximal exercise heart rate, which occurred to the same extent in both groups, have both been associated with lower coronary heart disease mortality.[1,2] In any event, higher values of VO_2 max would almost certainly have been achieved by a study period >8 weeks.

In the studies of Paffenbarger[3] and Leon[4] and their co-workers, in which exercise reduced coronary risk, leisure time physical activity was performed *primarily* in bouts of substantially <10 minutes each. Indeed, aggregate measures of leisure time physical activity in both studies more closely approximated 3 short bouts than a single long bout of exercise. In light of such data, it is hard to understand LaFontaine and Robbins' apparent enthusiasm for longer bouts of exercise as a method to reduce coronary risk.

The notion that only exercise training bouts of ≥20 to 30 minutes bestow physiologic or clinical benefits stems in large part from the circumstances in which exercise training has been conducted in research laboratories. In that environment, it is distinctly more efficient to train individuals in single 20- to 30-minute bouts than in multiple bouts as short as 10 minutes. However well justified such a policy may be in research, it is overly restrictive as the basis for advice to the public. If patients hear from physicians and other authorities that only exercise performed continuously for 20 to 30 minutes produces health benefits such as increased functional capacity, they are likely to conclude that anything less is ineffective. And that would be wrong.

The nub of the issue is well expressed by LaFontaine and Robbins in the last sentence of their letter: "Therefore, continuous 30-minute bouts of aerobic exercise, performed 5 days/week . . . are preferred over three 10-minute bouts." The question is, preferred by whom? Certainly not by the public: Trends toward greater participation in physical exercise by Americans during the past 2 decades have stabilized or reversed.[5,6] Even the staunchest defenders of the One True Church of 30-minute exercise bouts 5 times per week must have noted a shrinking of the congregation, in part because the public has moved to more convenient and enjoyable regimens. We believe that many people would be encouraged to participate in regular physical exercise if they perceived a benefit from shorter bouts of exercise. In any event, it is for the people themselves to decide which regimens are preferable. LaFontaine and Robbins may be surprised to learn that the public's overriding interest in exercise focuses not on increased functional capacity, but on weight reduction and weight maintenance. The caloric effects of short and long bouts of exercise are virtually identical and the degree of weight loss in this study—2 pounds over 8 weeks—reflects this.

In the era of glasnost, it would be inappropriate for the medical profession to ignore the needs of a public desperately striving to break the shackles of obesity and physical inactivity. Will we provide them all available means for doing so, or will we ourselves be shackled by a tyrannic orthodoxy?

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William L. Haskell, PhD
Palo Alto, California
27 August 1990

1. Blair SN, Kohl HW III, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395–2401.
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Can the Dipyridamole-Doppler Stress Test Detect Myocardial Ischemia?

Agati et al[1] report that Doppler interrogation of aortic flow during dipyridamole stress is highly sensitive in the detection of myocardial ischemia. Numerous exercise-Doppler studies have emphasized the limitations of this approach in detecting coronary artery disease (CAD).[2] We would like to make the following points.

First, the aim of the study was to establish whether the dipyridamole-Doppler test could detect myocardial ischemia and yet this question remains unanswered. Experimental and clinical attempts to use Doppler indexes to do this have failed, except in special situations such as during percutaneous transluminal coronary angioplasty or during coronary ligation studies in animals.[3] To answer the question, CAD patients who developed ischemia during the test need to be compared with well-matched CAD patients who did not, whereas Agati et al compared their CAD group (some of whom did not develop ischemia) with a control group.

Second, 3 group II patients showed an increase in Doppler parameters despite the occurrence of new wall motion abnormalities, which the authors speculate could have been due to the development of compensatory hyperkinesia in normal myocardial segments. Was this seen in these patients or in any of the others with wall motion abnormalities?

Third, although no CAD patient had a pretest wall motion abnormality, the baseline ejection fraction is not given; because 22 of 29 CAD patients had multivessel CAD, this is likely to have been abnormal in a proportion. Impaired pretest left ventricular systolic and diastolic function could account for the increase in left ventricular end-diastolic pressure, decrease in stroke volume and minimal change in peak positive left ventricular dP/dt induced by dipyridamole in the CAD group. These changes could therefore represent the interaction of a hemodynamic change with an abnormal ventricle rather than be a manifestation of myocardial ischemia. Similarly, patients with a higher coronary angiographic jeopardy score may have had poorer left ventricular function, which would account for the apparently higher sensitivity of Doppler variables in this subgroup.

Last, baseline (temporal) variability is generally greater than intraobserver and interobserver variability (because it incorporates intraobserver, physiologic and technical variation) and is much more relevant to serial measures, but is not quoted.

We studied 40 patients during dipyridamole stress and compared CAD patients who developed ischemia with those who did not using 2-dimensional echocardiographic and electrocardiographic criteria.[4] Groups were well-matched for baseline left ventricular systolic and diastolic function. Doppler indexes of aortic flow were insensitive in detecting ischemia; similar negative conclusions have been reached by others.[5] We observed a highly variable response to dipyridamole between patients, resulting in considerable overlap in the changes in Doppler indexes between groups. We also found that Doppler parameters of global left ventricular systolic function are generally preserved in the setting of localized ischemia unless ischemia is profound or associated with left ventricular dilatation. The effect of the marked drop in systemic vascular resistance induced by dipyridamole on aortic flow probably overrides the effect of localized transient left ventricular dysfunction, which is, in any case, compensated for by hyperkinesia of nonischemic myocardium, a common observation in our patients.

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18 June 1990

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Cardiac Transplantation and Cancer

In their recent article, Edwards et al[1] concluded that a history of neoplastic disease need not serve as a contraindication to cardiac transplantation. However, we feel that their results do not support this conclusion. It must be noted that the total number of patients is small (n = 7) and the selection criteria are not clear. Despite "careful" selection, overall survival at 1 year was 57%, which compares poorly with the overall survival figures of 85% at 1 year quoted by the International Society for Heart Transplantation.[2] The type and extent of malignant disease must be evaluated with care. It appears inappropriate to transplant a patient with a Duke's stage C2 adenocarcinoma of the colon when this stage of disease has a known 5-year survival of only 10 to 20%.[3] In addition, 1 patient underwent retransplantation after recurrent rejection episodes. The results for early retransplantation are poor[4] and in our view it is difficult to justify this management. It is not sufficient to assess only cardiotoxic effects of chemotherapeutic agents and radiotherapy without considering other systemic side effects, including pulmonary disease. Treatment-related respiratory failure was the cause of death in 1 patient and suggests inadequate preoperative assessment.

We agree that transplantation is feasible in carefully selected patients who are "cured" after treatment of malignant disease, but is it a prudent use of scarce donor resources? It is not our practice to transplant patients who are known to have malignancy.

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Atrial Septal Aneurysm as a "Newly Discovered" Cause of Stroke in Patients with Mitral Valve Prolapse

The recent report of an increased prevalence of atrial septal aneurysm (ASA) in mitral valve prolapse (MVP)[1] has important clinical implications besides establishing a definitive association. The latter was first brought to our attention in 1984.[2,3]

ASA is often associated with interatrial shunting,[4,5] which can, in turn, lead to paradoxical embolism.[6] Systemic embolism, especially into the cerebral circulation, is one of the serious complications of MVP, which is otherwise a benign and common condition.[7] The most likely cause of cerebral ischemic attacks and strokes in patients with MVP is embolism of a noninfective contact thrombus, originating either from the atrial surface of the prolapsing mitral leaflet or in the angle formed by the junction of the left atrial endocardium and the atrial surface of the prolapsing posterior leaflet.[8] Now a new cause has been found—namely, ASA.

Clinical diagnosis of ASA in a patient with MVP is difficult, because a midsystolic click, which is the only auscultatory clue to the presence of ASA,[9] is a common finding in MVP. The recent surge in the reported prevalence of ASA is certainly the result of increased use of echocardiography, both precordial[10] and transesophageal,[11] and increased awareness of the entity. The true prevalence of interatrial shunting in ASA might have been underestimated before the routine use of contrast echocardiography in conjunction with performance of the Valsalva maneuver.[6,12,13]

This "newly discovered" cause of stroke in patients with MVP also has an important therapeutic implication. The embolic risk here would make what would otherwise have been a simple anatomic curiosity a potentially serious anomaly. This has led some authors to propose surgical repair of ASA associated with systemic embolism, irrespective of its size, in order to prevent the risk of embolic recurrence and to avoid the need for lifelong anticoagulant therapy.[14]

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30 July 1990

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Interaction Between Amiodarone and Phenytoin

Nolan et al[1] reported an interaction between phenytoin and amiodarone. Although they clearly demonstrated an interaction between amiodarone and phenytoin (probably involving enzyme inhibition), we are concerned about some of the conclusions drawn.

First, the recommendation that a dosage reduction of phenytoin by 25 to 30% be made after the addition of amiodarone may lead to serious errors. Phenytoin displays Michaelis-Menten (MM) kinetics (at therapeutic concentrations)[2] and a 25% dosage reduction would, by the equation below, reduce the plasma concentration by 50 to 75%, from 10 and 20 mg/liter, respectively:

$$Css = \frac{dose/day \times Km}{Vm - dose/day}$$

This could lead to poor control of epilepsy or arrhythmias, and possibly to withdrawal symptoms. According to the equation, Nolan et al should have recommended a dose reduction of only 10% to maintain the mean concentrations of phenytoin before the addition of amiodarone (6.7 mg/liter).

Second, quoting clearances has little relevance to drugs that display MM kinetics, because the elimination rate is variable, depending on serum concentration.

Third, the study title included the term "steady-state," which may be misleading because amiodarone has a half-life of 25 ± 12 days[3] and would not be expected to be at steady state at the time of the study. If steady state had been achieved, the degree of enzyme inhibition may well have been greater than that seen.

We conclude that the data presented by Nolan et al is sufficient only to prove that an interaction does exist and that a dosage reduction of phenytoin may be required. Clearly this is a case for increased therapeutic drug monitoring and not for specific guidelines that are inappropriate.

S.B. Duffull
S.K. McKenzie
Christchurch, New Zealand
2 August 1990

1. Nolan PE Jr, Erstad BL, Hoyer GL, Bliss M, Gear K, Marcus FI. Steady-state interaction between amiodarone and phenytoin in normal subjects. *Am J Cardiol* 1990;65:1252–1257.
2. Winter ME, ed. Basic Clinical Pharmacokinetics. Washington: Applied Therapeutics, 1983:184–187.
3. Mammen GJ, ed. Clinical Pharmacokinetics Drug Data Handbook, 2nd edition. Auckland, New Zealand: Adis Press, 1990:40.

REPLY: We thank Duffull and McKenzie for their comments regarding our investigation and conclusions. We arrived at our recommendation of an initial 25 to 30% reduction in phenytoin doses when concomitant amiodarone is instituted in the following way. Grech-Belanger demonstrated that the depressive effect of amiodarone on aromatic ring hydroxylation occurred via competitive inhibition.[1] In that phenytoin principally undergoes aromatic ring hydroxylation to form 5-(p-hydroxyphenyl)-5-phenylhydantoin,[2] we assumed that amiodarone competitively inhibited phenytoin metabolism. When competitive inhibition of substrate (i.e., phenytoin) metabolism occurs, the Km of the metabolic reaction is increased.[2] Km is the concentration at which substrate metabolism is 50% of Vm, the maximum rate of substrate metabolism. Therefore, in the equation presented by Duffull and McKenzie, the observed steady-state increases in serum phenytoin concentrations during concomitant phenytoin and amiodarone treatment should have occurred in proportion to the amiodarone-mediated increases in the Km of phenytoin. The percent decrease in the dose of phenytoin required to maintain pre-amiodarone serum concentrations is variable, but dependent upon both the baseline Km and the percent increase in Km caused by amiodarone. For example, assuming an average Vm of 7 mg/kg/day,[2] and using the mean daily dose of phenytoin of 250 mg/day, a calculated Km of 7.4 μg/ml would be expected from our pre-amiodarone mean concentration of 6.7 μg/ml. To achieve our observed mean phenytoin concentration of 10.3 μg/ml after the addition of amiodarone, the calculated Km is 11.4 μg/ml, a 54% increase from baseline. A 22% reduction in the daily dose of phenytoin would therefore be required to achieve the pre-amiodarone concentration of 6.7 μg/ml. It appears from their calculations that Duffull and McKenzie used average estimates of Km and Vm, 4 μg/ml and 7 mg/kg/day,[2] respectively, but did not take into account any changes in the Km of phenytoin during coadministration with amiodarone. Interestingly, in the first case report by McGovern et al,[3] their patient required a 33% reduction in the dose of phenytoin when concurrently receiving amiodarone in order to achieve serum concentrations of phenytoin similar to those with phenytoin alone.

Second, we do agree with Duffull and McKenzie that clearance is a term most appropriately reserved for drugs that display first-order rather than Michaelis-Menten (MM) pharmacokinetics. However, in our paper we purposefully used the term "approximate oral clearance for phenytoin" in order to convey to readers that we were only estimating the clearance of phenytoin, a drug that demonstrates nonlinear or MM kinetics. For drugs that demonstrate MM kinetics, Cheng and Jusko[4] discuss the concept of a "time-averaged clearance," which varies inversely in relation to dose, and which can be calculated in a manner similar to how clearance is calculated for a drug following first-order kinetics.

Third, we did not intend to mislead readers with the term "steady-state." Based on the study by Gugler et al,[5] the phenytoin concentrations at the doses we administered should have been at steady state after 14 days of dosing. We do agree that amiodarone concentrations after 6 and one-half weeks (i.e., 45 to 46 days) of daily administration of amiodarone were probably not at steady state. However, if an average half-life of 25 days is assumed for amiodarone, then our subjects were approximately at 75% of steady state, assuming amiodarone follows first-order pharmacokinetics.

In conclusion, we feel that a 25% reduction in the daily dose of phenytoin for patients receiving 3 to 4 mg/kg/day is a reasonable initial estimate when amiodarone is concurrently administered. We reiterate that changes in phenytoin dosage regimens during coadministration with amiodarone should ultimately be guided by a combination of the clinical condition of the patient and by the serum concentrations of phenytoin.

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19 September 1990

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The Sleep Electrocardiogram at Extreme Altitudes

I found the article by Malconian et al[1] to be informative and interesting and would like to add to their report my experience in this field. As reported,[2] I had the opportunity to examine a Holter recording in a subject who climbed, in the summer of 1983, the northern face of K2. During this recording he spent a night at a bivouac at about 8,200 meters above sea level. I observed, while he slept at this altitude, sudden and cyclic variations of heart rate with periods characterized by junctional rhythm (45 beats/min) and sinus rhythm (65 beats/min) in the absence of any tachyarrhythmias (see our Figures 6 and 7).[2] This case confirms completely the data obtained by Malconian et al in the hypobaric chamber.

Gianfranco Buja, MD
Padova, Italy
8 August 1990

1. Malconian M, Hultgren H, Nitta M, Anholm J, Houston C, Fails H. The sleep electrocardiogram at extreme altitudes (Operation Everest II). *Am J Cardiol* 1990;65:1014–1020.
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Right Ventricular Diastolic Function in Children

Although we found the data presented by Vermilion et al[1] interesting, we believe their approach to the analysis of right ventricular (RV) diastolic filling may be oversimplistic and would advise caution in the interpretation of their data regarding the isolated analysis of tricuspid A-wave velocity and velocity integral in patients after relief of RV outflow tract obstruction. Indeed, these changes may be uninterpretable in the absence of a detailed analysis of the pattern of pulmonary artery flow. The accompanying figure shows the pulmonary artery flow pattern of 1 of 4 patients whom we studied after complete relief of RV outflow tract obstruction for pulmonary atresia with intact septum. Although there was a dominant A wave on the tricuspid inflow Doppler, it is almost wholly accounted for by forward flow into the pulmonary artery coincident with atrial systole. Thus, late RV diastolic filling may be markedly restricted in the presence of a large A wave on the tricuspid inflow Doppler, the right ventricle acting as a conduit between the right atrium and the pulmonary artery in late diastole. E-wave deceleration time, and its change with respiration, may yield important additional information in such patients,[2] and should also have been measured in the patients presented by Vermilion et al. It is possible that large changes in diastolic function occurred despite little change in A-wave velocity after balloon valvuloplasty. There are clearly diastolic abnormalities in these patients with severe RV outflow tract obstruction but the exact nature of these abnormalities has yet to be determined.

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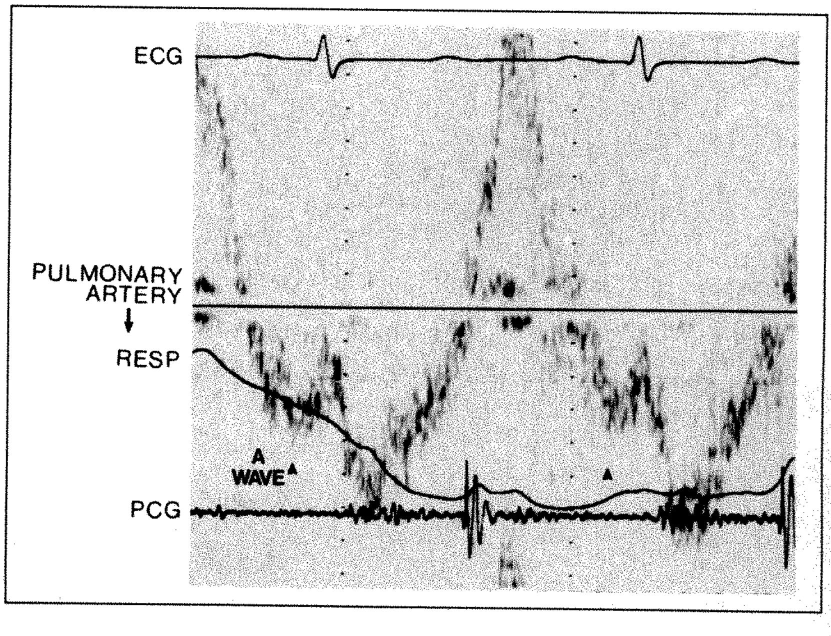
10 August 1990

1. Vermilion RP, Snider AR, Meliones JN, Peters J, Merida-Asmus L. Pulsed Doppler evaluation of right ventricular diastolic filling in children with pulmonary valve stenosis before and after balloon valvuloplasty. *Am J Cardiol* 1990; 66:79–84.
2. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:757–768.

REPLY: The comments made by Redington and colleagues are intriguing but largely unrelated to our recent article on right ventricular (RV) diastolic filling in children with isolated pulmonary valve stenosis.[1] We agree that an isolated analysis of tricuspid valve peak A velocity and A area fraction is inadequate to assess RV diastolic filling. For this reason, our study included measurements of indexes of early diastolic filling such as peak E velocity, first-third area fraction, E area fraction, and peak filling rate normalized for stroke volume. We disagree with Redington et al's statement that RV diastolic function cannot be assessed in the absence of a detailed analysis of the pattern of pulmonary artery flow. In our experience, analysis of the pulmonary artery Doppler wave



form is only helpful in those patients in whom the right ventricle is underdeveloped and serves as a passive conduit between the right atrium and pulmonary artery in late diastole. Patients with diastolic forward flow in the pulmonary artery during right atrial contraction have an obviously abnormal and noncompliant right ventricle and do not constitute a group of patients in whom one needs to measure the tricuspid valve inflow Doppler to assess diastolic function. On the other hand, we have found that the analysis of a systemic vein Doppler recording can provide very important additional information in the assessment of RV diastolic function.

Changes in the tricuspid valve Doppler caused by structural abnormalities of the tricuspid valve cannot easily be distinguished from those caused by altered diastolic function. For this reason, patients with tricuspid valve stenosis or underdevelopment of the RV inflow, or both, were excluded from our study. The figure supplied by Redington et al simply illustrates that the tricuspid valve Doppler recordings reflect many factors, including structural abnormalities of the tricuspid valve or right ventricle, right atrial compliance, changes in intrathoracic pressure, and so forth. We would not expect the tricuspid valve Doppler recording to reflect RV diastolic function in patients with hypoplastic right heart any more than we expect the mitral valve Doppler recording to reflect left ventricular diastolic function in hypoplastic left heart. This fact and the case cited by Redington et al do not negate the usefulness of the tricuspid valve Doppler for the assessment of diastolic function in children with no tricuspid valve stenosis, a normally formed right ventricle and isolated pulmonary valve stenosis.

Finally, we agree with Redington et al that analysis of RV diastolic function should include some measurement of the rate of RV relaxation in early diastole. Certainly, the deceleration time is one of several equally useful indexes of early RV filling.[2] In our study, we chose to use the peak filling rate normalized for stroke volume as an index of the rate of early relaxation. Because of the normalization to stroke volume, the peak filling rates of children of different body sizes and ages can be easily compared. This is not the case for the deceleration time, which varies with the varying heart rates encountered among children of different ages. Furthermore, because peak filling rate did not change after successful balloon valvuloplasty, it is not likely (as Redington et al suggest) that large changes in diastolic function occurred despite little change in peak A velocity.

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27 August 1990

1. Vermilion RP, Snider AR, Meliones JN, Peters J, Merida-Asmus L. Pulsed Doppler evaluation of right ventricular diastolic filling in children with pulmonary valve stenosis before and after balloon valvuloplasty. *Am J Cardiol* 1990; 66:79–84.

2. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988; 12:426–440.

Sudden Death Associated with Exercise: The Risk-Benefit Issue

Friedewald and Spence's[1] article is useful and sensible. However, the thrust of their argument will lead to an overuse of exercise tolerance testing in persons who really do not need it—a strategy, which, if widely applied, will be very expensive and nonproductive.

A much simpler, inexpensive and well-validated instrument[2,3] has been shown to be a reliable preexercise screening tool for middle-aged persons, likely the group of greatest concern. This instrument has been validated and subsequently widely used in this country.

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Saskatoon, Canada
13 August 1990

1. Friedewald VE Jr, Spence DW. Sudden cardiac death associated with exercise: the risk-benefit issue. *Am J Cardiol* 1990;66:183–188.

2. Chisholm D, Collis M, Kulak L, Davenport W, Gruber N, Stewart G. PAR-Q Validation Report: The Evaluation of a Self-Administered Pre-Exercise Questionnaire for Adults. Canada: British Columbia Ministry of Health, and Health & Welfare, 1978.

3. Firor WB, Faulkner RA. Sudden death during exercise: how real a hazard? *Can J Cardiol* 1988;4:251–254.

REPLY: We appreciate Dr. Firor's comments. The Physical Activity Readiness Questionnaire (PAR-Q) has been used widely in Canada as a self-administered, preexercise screening instrument. The sensitivity and specificity of the PAR-Q is reported to compare favorably with other screening procedures; however, its sensitivity in predicting an abnormal exercise electrocardiogram is weak.[1] On balance, we feel that the PAR-Q has merit principally as a tool for preexercise mass screening, rather than for assessment of individual patients who, for some reason, are seeking personal medical advice.

The bent of our article was toward the latter circumstance, i.e., the individual patient seeking exercise advice. Such patients represent a population that is self-selected and perhaps at higher risk than the general population. From this perspective, we feel that initial cardiovascular screening of middle-aged and older persons who wish to exercise should be conducted by the physician who can weigh risk versus benefit for an individual patient. For these patients, the exercise risk issue may be too problematic to be addressed by a self-administered questionnaire.

Therefore, although we agree that exercise testing is not cost effective for mass screening, there is no adequate substitute for a good history and physical examination by a physician, followed by an exercise test when clinical judgment warrants it. Sudden cardiac death is too important to be paid any less attention when our patients ask for our best advice.

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17 September 1990

1. Shephard RJ. Can we identify those for whom exercise is hazardous? *Sports Med* 1984; 1:75–86.

Subgroup Analysis of Clinical Trials

The editorial by Yusuf et al[1] with regard to our report[2] raises major questions about the use of subgroup analysis of clinical trials. Clinical trials are by their nature isolated experiments in clinical therapy. We agree with Dr. Yusuf in his assessment that subgroup analysis of this type of experiment is fraught with danger. Clinical trials, however, represent an opportunity to understand the natural history of a disease process and to raise certain hypotheses that can be tested in the future.[3,4] We are concerned that Yusuf's approach will discourage others from carrying out exploration in the future, and valuable information may be lost. To limit one's observations and comments in regard to a clinical trial to only the primary objectives is to miss an opportunity to understand and question current and future approaches to medical therapy. In fact, a wealth of clinical information has been generated from these trials. Certainly one must proceed with great caution and forewarn the reader, as we did in our article. We stated clearly that this was a "hypothesis-generating project and that definitive conclusions regarding therapeutic β-adrenergic blocking agents in survivors of non-Q-wave acute myocardial infarction cannot be made."

A multitude of subgroup analyses have been performed not only in the Beta Blocker Heart Attack Trial (BHAT), but also in many other clinical trials examining the efficacy of this class of drugs. We agree that, in general, they all support the general thesis that β-adrenergic blocking agents are beneficial to patients with coronary artery disease. It would, however, be misleading to present only those subgroup analyses that confirm the positive aspects of the trial. Yusuf and colleagues argue for consistency in evaluating subgroups of clinical trials. Consistency, however, has the potential of becoming dogma.

It is clear that our understanding of coronary artery disease and its different modes of presentation has changed dramatically in the last 3 decades. Much of this understanding emanates from the examination of clinical trials and is achieved only by examining the effect of a pharmacologic probe, such as propranolol, on a disease process. In the evaluation of our article, Yusuf failed to recognize that, since the completion of the BHAT, a substantial amount of evidence now supports the prognostic importance of dividing myocardial infarctions based on the presence or absence of abnormal Q waves.[5] It was precisely for this reason that our analysis was initiated. It should not be presumed that it was a biostatistical fishing expedition, as implied by Yusuf.

In response to the specific criticism, Yusuf et al indicate that:

1. There were only a small number of patients in this subgroup. In fact, a total of 601 patients are included, representing approximately 15% of all patients enrolled in the BHAT. We judge this to represent a substantial part of the overall enrollment in that trial.

2. Our results are directly contradicted by the Timolol Trial results. The Norwegian Timolol Trial subgroup analysis[6] suggested that timolol was beneficial in patients with a "nontransmural" myocardial infarction. However, the diagnosis of "nontransmural" myocardial infarction was made from the baseline electrocardiogram, yet the randomization occurred 7 to 28 days after the event. This is particularly relevant because, since the initial electrocardiogram in the BHAT, 263 patients (30%) of the nontransmural myocardial infarction population developed significant Q waves by the time of randomization. This led to the reclassification of patients initially presumed to have experienced a non-Q-wave infarction, and is in fact the essence of our analysis. Huey et al[7] emphasized the difficulty in diagnosing a Q- and a non-Q-wave myocardial infarction from the admission electrocardiogram. The diagnosis of non-Q-wave acute myocardial infarction can be made reliably if Q waves or Q-wave equivalents do not develop over 24 to 72 hours after the onset of infarction.[8]

3. Evidence of benefit in non-Q-wave myocardial infarction is supported by the trials of early intravenous β blockers in acute myocardial infarction. On the contrary, the only randomized trial that differentiated Q- from non-Q-wave myocardial infarction was the Metoprolol in Acute Myocardial Infarction Trial,[9] which showed that the 15-day mortality rate was higher in the metoprolol-treated non-Q-wave acute myocardial infarction patients when compared with placebo (28 of 565 [5%] vs 17 of 537 [3.2%], respectively). The statement by Yusuf et al that patients with suspected myocardial infarction without ST elevation clearly benefit by early intervention with β blockers is also not supported by the 2 references he quotes. The Goteborg Metoprolol Trial[10] does not provide data on the efficacy of β blockade in patients with acute myocardial infarction presenting with ST depression. In the First International Study of Infarct Survival,[11] patients with suspected acute myocardial infarction without ST elevation had a mortality at 7 days of follow-up after their index myocardial infarction of 1.1% (15 of 1,318) in the atenolol group and 1.2% (17 of 1,368) in the control group.

We therefore believe that the treatment with β-adrenergic blocking agents has had a profound effect on the morbidity and mortality of coronary artery disease. Nevertheless, it is possible that their relative inefficacy in non-Q-wave myocardial infarction may indicate that a different pathophysiologic process is in progress in this clinical syndrome. As Yusuf states, our findings "should be tested in other related studies." We hope that our analysis will stimulate such analysis. If our observations are replicated, this may add to our understanding of the pathogenesis of coronary artery disease.

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Lonni Schultz, MS
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13 August 1990

1. Yusuf S, Wittes J, Probstfield J. Evaluating effects of treatment in subgroups of patients within a clinical trial: the case of non-Q-wave myocardial infarction and beta blockers. *Am J Cardiol* 1990;66:220–222.
2. Gheorghiade M, Schultz L, Tilley B, Kao W, Goldstein S. Effects of propranolol in non-Q wave acute myocardial infarction in the Beta Blocker Heart Attack Trial. *Am J Cardiol* 1990;66:129–133.
3. Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. *N Engl J Med* 1987;317:426–432.
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8. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghiade M, Capone RJ, Crawford MH, Schlant RC, Kleiger RE, Young PM, Schechtman K, Perryman B, Roberts R, and the Diltiazem Reinfarction Study Group. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986;315:423–429.
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11. ISIS-I (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986;2:57–66.

REPLY: Before a treatment is shown to be effective, the burden of proof is on those who claim efficacy. Once benefit of treatment is demonstrated conclusively, however, the burden of proof shifts. A claim that a treatment already clearly shown beneficial is ineffective in a specific subgroup of patients must be strongly supported by data. How should researchers react when confronted with compelling data from large studies and seemingly contradictory data from a small subgroup? When should the trend in a subgroup be regarded as prescriptive of alternative treatment, when should it be considered as generating a new hypothesis, and when should it be ignored because it is likely to be spurious?

A clinical trial, or an analysis of a subgroup within a trial, is *not* an isolated experiment in clinical therapy. The response to a treatment in a subgroup of a clinical trial is more likely to be in the same direction as in the entire group than to be of no effect or of opposite effect.[1] Thus, an apparent discrepancy should be viewed with caution, and not, of course, dismissed out-of-hand, but subject to critical questioning. Inference about a subgroup should be linked formally to the larger body of data of which the subgroup is a part. That larger body may be data from the other patients in the trial itself or data from similarly treated patients in other randomized, controlled trials. Several statistical approaches formally place subgroup effects in the context of such overall data. Examples of these methods include tests for interaction, Bayesian estimation of the posterior distribution of the subgroup effect with a prior hypothesis that relates to the observations at large, and empirical Bayes techniques to pull the subgroup estimates of treatment effect toward the overall mean.[2,3]

Gheorghiade et al[4] in their report and in their letter note that the subgroup of patients in the BHAT with non-Q-wave myocardial infarctions show no reduced mortality when randomized to β blockers; they consider this observation to generate the hypothesis that β blockers are ineffective in such patients. Gheorghiade et al use no formal approach for analysis of the subgroup; rather, they simply examine, in isolation, the subgroup of patients with non-Q-wave infarctions. Then, without formal reference to the overall results of the BHAT, they perform a test of significance, find no difference in mortality rates between treated and control groups, and declare they have generated a hypothesis. This approach, if widely applied, would produce a host of hypotheses that turn out to be false.

Although Gheorghiade et al consider the subgroup of 601 non-Q-wave patients to represent "a substantial part of the overall enrollment," this subgroup is too small to generate useful hypotheses regarding the effects of treatment. A rational method of deciding whether a subgroup is "large" is to calculate the power against a reasonable hypothesis. Data from 24 trials studying a total of 20,000 patients suggest that β blockers would reduce mortality and reinfarction overall by 20 to 25% and therefore by a similar amount in any specific subgroup. As we indicated in our editorial,[5] even using the approach of Gheorghiade et al, the power to detect a 25% reduction in mortality with 601 patients is very low, roughly 15%. In fact, if the reduction were 25%, the probability would be roughly 1 of 5 that a subgroup of 601 would show an effect as small or smaller than that observed by Gheorghiade et al. Thus, the fact that they found no treatment effect for β blockers is hardly surprising, because the sample size is quite small in relation to the effect one reasonably would expect.

Of course, as long as valid analytical methods are used, subgroup hypotheses worth testing can be generated from data of clinical trials.

Janet Wittes, PhD
Washington, D.C.
Salim Yusuf, MB, MRCP, DPhil
Jeffrey L. Probstfield, MD
Bethesda, Maryland
28 September 1990

1. Yusuf S, Held P, Teo KK, Toretsky ER. Selection of patients for randomized controlled trials: implications of wide or narrow eligibility criteria. *Stat Med* 1990;9:73–86.
2. Simon R. Patient subsets and variation in therapeutic efficacy. *Br J Clin Pharmacol* 1982;14:473–482.
3. Davis CE, Leffingwell DP. Empirical Bayes estimates of subgroup effects in clinical trials. *Controlled Clin Trials* 1990;11:37–42.
4. Gheorghiade M, Schultz L, Tilley B, Kao W, Goldstein S. Effects of propranolol in non-Q-wave acute myocardial infarction in the Beta Blocker Heart Attack Trial. *Am J Cardiol* 1990;66:129–133.
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Treatment Algorithms for Patients with Ventricular Arrhythmias

I read with interest the editorial on "Pharmacologic Management of Ventricular Arrhythmias After the Cardiac Arrhythmia Suppression Trial" by Morganroth and Bigger.[1] The editorial largely focuses on the treatment of patients with frequent or complex ventricular ectopic activity and only a small amount of attention is focused on patients with sustained ventricular tachycardia or cardiac arrest. However, the algorithm for treatment of ventricular arrhythmias in Figure 1 does include patients with these latter arrhythmias, and I believe this portion of the flow diagram is potentially misleading.

It has been well shown that only 30 to 50% of patients who present with sustained ventricular tachycardia or ventricular fibrillation in the context of chronic coronary artery disease will have their arrhythmias suppressed—by electrophysiologic criteria—by any drug therapy currently available.[2] For many of these patients, the use of nonpharmacologic therapy is the key to successful long-term management. A small segment of patients will have discrete, resectable aneurysms and mappable tachycardias. In properly selected patients, surgical mortality is low and the success rate for arrhythmia control high.[3] In these patients, surgical therapy may be the optimal approach and drug trials would not be indicated. Other patients will best be managed with implantable cardioverter defibrillators, either with or without adjunctive drug therapy.

The use of implantable cardioverter defibrillators had made a dramatic impact on our ability to manage patients with malignant arrhythmias. Although controlled studies are lacking, there is little disagreement with the data presented by Tchou et al[4] and others[5,6] showing an impressive reduction in total mortality in patients who received these devices. These devices continue to be improved upon and we should expect them to play an even greater role in preventing sudden death in the future.

We are now at the point where most chronic arrhythmias in otherwise stable patients can be successfully treated but the optimal approach requires that we use *all* available modes of therapy. In light of our previous experience with new antiarrhythmic drugs, it seems more likely that the indications for nonpharmacologic therapy will broaden rather than be decreased by refinements in drug treatment.

John P. DiMarco, MD, PhD
Charlottesville, Virginia
20 August 1990

1. Morganroth J, Bigger JT Jr. Pharmacologic management of ventricular arrhythmias after the Cardiac Arrhythmia Suppression Trial. *Am J Cardiol* 1990;65:1497–1503.
2. Rae AP, Greenspan AM, Spielman SR, Sokoloff NM, Webb CR, Kay HR, Horowitz LN. Antiarrhythmic drug efficacy for ventricular tachyarrhythmias associated with coronary artery disease as assessed by electrophysiologic studies. *Am J Cardiol* 1985;55:1494–1499.
3. Cox JL. Patient selection criteria and results of surgery for refractory ischemic ventricular tachycardia. *Circulation* 1989;79(suppl I):I-163–I-177.
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In the editorial entitled "Pharmacologic Management of Ventricular Arrhythmias After the Cardiac Arrhythmia Suppression Trial" by Morganroth and Bigger,[1] there is an algorithm for the treatment of ventricular arrhythmias in Figure 1. I was perplexed that the evaluation provided for the benign and potentially malignant arrhythmias did not include exercise testing but only Holter monitoring. It has been reported that exercise provocation of arrhythmias may determine suppressibility as well as proarrhythmia. I am somewhat dismayed by the absence of exercise testing in the CAST trial, as well as that the physicians involved in the trial continue to eliminate exercise testing. Most patients have associated coronary artery disease, and exercise testing, albeit imperfect for provocation of arrhythmias, does have certain advantages with regard to risk, based on left ventricular function and degree of ischemia as well. Any comments on the exclusion of exercise testing by the authors would, I am sure, be appreciated by many in the field who are interested in sudden death.

Charles L. Baird, Jr., MD
Richmond, Virginia
30 August 1990

1. Morganroth J, Bigger T. Pharmacologic management of ventricular arrhythmias after The Cardiac Arrhythmia Suppression Trial. *Am J Cardiol* 1990;65:1497–1503.

REPLY: As the title of our editorial indicates, our purpose was to examine the impact of CAST on *pharmacologic*, not nonpharmacologic management, of potentially malignant ventricular arrhythmias. Stimulated by our diagram of pharmacologic management algorithms, Dr. DiMarco raises some important issues about *nonpharmacologic* treatment for patients with malignant ventricular arrhythmias and suggests that devices deserve a more prominent role. One general lesson that we learned from CAST is that conventional wisdom and practice may surprisingly not prove beneficial when evaluated by controlled clinical trials. Treatments that are actually harmful can look effective and safe when used in conventional practice. Clinicians are especially forgiving in their evaluation of treatments that are used as a last resort (*sic* amiodarone).

The early experience with implantable cardioverter defibrillators is encouraging, even in very sick patients. Implantable cardioverter defibrillators can detect and terminate sustained ventricular tachycardia or ventricular fibrillation. The sudden cardiac death rates of patients treated with implantable cardioverter defibrillators in specialized arrhythmia centers is so low as to suggest that the treatment is effective even without a randomized, controlled trial.

The picture is not clear for the effect of implantable cardioverter defibrillators on *total* mortality. The data available suggest a substantial reduction in nonarrhythmic as well as arrhythmic death rates in patients with malignant ventricular arrhythmias treated with implantable cardioverter defibrillators. Although several explanations are possible for this finding, these data suggest that selection of malignant arrhythmia patients for implantable cardioverter defibrillator treatment may exclude the sickest patients. Certainly, it is impossible to draw firm conclusions from available data about the effect of implantable cardioverter defibrillators on total mortality relative to other treatment options. To establish the superiority of implantable cardioverter defibrillator treatment over alternative treatments will require randomized, controlled trials, especially if implantable cardioverter defibrillator treatment is to be positioned as a first-line or mid-range therapy, rather than as a last resort.

Fortunately, there are ongoing trials that will shed light on the efficacy of implantable cardioverter defibrillator treatment relative to drugs currently used for the treatment of malignant ventricular arrhythmias. For example, the Hamburg trial is randomizing patients with malignant ventricular arrhythmias to 1 of 3 drug limbs (metoprolol, propafenone, amiodarone) or to implantable cardioverter defibrillator treatment. The Canadian Implantable Defibrillator Trial sponsored by the Medical Research Council is now randomizing patients with documented malignant ventricular arrhythmias to amiodarone or to an implantable cardioverter defibrillator treatment.

These 2 randomized, controlled trials will help to position implantable cardioverter defibrillator treatment against pharmacologic alternatives on the basis of data rather than judgment and conjecture. Until controlled data are available, the current diversity in approaches to management of malignant ventricular arrhythmias is likely to continue.

Additional studies are just underway to explore the use of implantable cardioverter defibrillator therapy in the management of potentially malignant ventricular arrhythmias, e.g., patients with left ventricular dysfunction and unsustained ventricular tachycardia (MADIT) or those with left ventricular dysfunction and a positive signal-averaged electrocardiogram (The CABG Patch Trial). The use of implantable cardioverter defibrillators for patients with potentially malignant ventricular arrhythmias presents many problems that can never be solved without a randomized, controlled trial.

Although implantable cardioverter defibrillator treatment is far from established as the premier treatment for malignant ventricular arrhythmias or as having a role in the management of potentially malignant ventricular arrhythmias, it is a tribute to the concept and to early experience that this mode of therapy has reached the stage where the resources required for a randomized, controlled trial are justifiably being committed.

Regarding Dr. Baird's letter, we agree that some have suggested recently (after the initiation of CAST) that exercise testing may be reasonably used in certain situations (e.g., to evaluate patient response to class IC antiarrhythmic drugs) as an end point for proarrhythmia and possibly arrhythmia suppression. However, there are no controlled clinical trials that establish its clinical usefulness. We do not think, therefore, that exercise testing should yet be considered as an absolute standard for inclusion in a patient management algorithm.

J. Thomas Bigger, Jr., MD
New York, New York
Joel Morganroth, MD
Philadelphia, Pennsylvania
13 September 1990

Bird Brains

The article by Dr. Diamond[1] was simply superb. It is an excellent application of game theories to science. However, the article reflects much more than that. It is also the opinion of Dr. Diamond on how to approach daily life. Dr. Diamond is obviously a "dove" scientist. His own beliefs may have introduced a source of bias that may have escaped his attention. The *"laissez faire"* approach will successfully deal with the problem if the value scales for hawks and doves are the same, as in Dr. Diamond's calculations. However, there must be a reason why hawks behave so aggressively. I believe the aggressivity is caused by a different value scale for the hawks. In case of a win, a hawk does not get +30 points. That win may represent as much as +480 points—that is, the same absolute number as the value of getting hurt. Wasting time does not exist for a hawk. The moderate win for a dove (+30 points) reflects a different approach to life. For a dove, indeed, all that counts is the acceptance of one's ideas. For a hawk, on the contrary, substantial gains may result from a win. Parallel situations in scientific life are easy to imagine when considering, for instance, material gains in relation to industry. I have not taken the time to recalculate Dr. Diamond's data using 2 different scales for hawks and doves. It is obvious, however, that the possible damage created by hawks may increase by a factor >10.

Like Dr. Diamond, I am also very confident in the *laissez faire* doctrine. But when the dangerous side of the population *fais* (does) too much and too aggressively (because of the expected profits), the whole population is rapidly endangered. That is the time to start a policy of *ne pas laisser faire* (do not allow to). Trust is not enough. Mechanisms must be created to identify the hawks and change them into doves, or to reduce the expected benefits of the hawks. It takes a hawk to recognize another hawk. Where will we doves find the first?

Pedro Brugada, MD
Aalst, Belgium
7 September 1990

1. Diamond GA. Bird brains: the evolution of scientific misconduct. *Am J Cardiol* 1990;66:372–374.

REPLY: I am gratified by Professor Brugada's thoughtful comments regarding my exposition of academic ornithology. He is indeed correct that changing the payoff values among hawks and doves will affect their survival, and I confess to having selected my values just to make a point (perhaps I am not the pedigree dove he thinks I am).

In fact, the academic aviary is populated by many more species than hawks and doves. In addition to the owls already mentioned in my essay, fellow birdwatchers have also sighted peacocks, parrots, pigeons, ostriches, turkeys, chickens, mockingbirds, dodos and coots (to name just a few). The social interactions among all these species are highly complex. So before substituting a doctrine of *ne pas laisser faire* for *laissez faire*, I believe we must first agree to protect the lone eagle and the lowly cuckoo from the more aggressive snipes (and even the snipes from the bird dogs). Accordingly, just as we have chosen to slant our legal system more toward protecting the innocent than punishing the guilty, I suggest we slant our academic system more toward protecting the doves than hunting the hawks.[1]

Consider the following parable in that light: "Imagine that you are on the editorial board of a prestigious. . .journal and that you receive a paper that is unorthodox in style and format. Its title has little to do with most of its content; it has no citations to current literature; a significant portion of its first half seems to be philosophical banter on the nature of certain basic. . .concepts taken for granted by everyone; the only experiment explicitly discussed could be explained adequately using current. . .theory and is not considered to be of fundamental importance." [2]

According to one recent source,[2] the editorial policy of *Annalen der Physik* in the early part of this century was based almost entirely on *laissez faire*. An author's initial contributions were reviewed by the Editor himself, or by a member of the Editorial Board. After that, subsequent papers were published with little or no refereeing. Public trial decided the merit of an idea. Given the conservative predisposition of many referees, Albert Einstein was indeed fortunate he had already published 8 articles in the *Annalen* by the summer of 1905,[3] because this allowed the outlandish relativity paper described above to be accepted for publication upon receipt. How might it be greeted today?

George A. Diamond, MD
Los Angeles, California
17 September 1990

1. Root-Bernstein RS. Discovering, Inventing and Solving Problems at the Frontiers of Scientific Knowledge. Cambridge, Massachusetts: Harvard University Press, 1989:382–405.
2. Miller AI. Imagery in Scientific Thought. Boston: Birkhauser, 1985:101,121.
3. Pais A. 'Subtle is the Lord. . .' The Science and the Life of Albert Einstein. New York: Oxford University Press, 1982.

Preoperative Imaging of the Internal Thoracic Artery

The study of Krijne et al[1] reports the low diagnostic yield of routinely imaging the internal thoracic artery (ITA) at the time of coronary arteriography. In their series of 105 patients undergoing coronary arteriography before coronary bypass surgery, only 1 (0.95%) had a significant stenosis in an ITA. Our experience in patients who have had previous sternotomy suggests that in these circumstances routine cannulation of the ITA may be indicated.

A prospective survey was undertaken of all patients undergoing coronary arteriography for possible intervention for recurrent angina after coronary bypass surgery. In all cases, saphenous vein grafts had been used without disturbing the ITA. Over 12 months, 82 such patients, who had previously received 1 to 4 vein grafts between 3 and 12 years, were studied.

The left ITA was successfully cannulated in all cases. In 2 cases (2.4%), the origin of the artery was from the third part of the subclavian artery rather than from the first part,[2] but the artery was of normal caliber and descended in the usual relation to the sternum. In 2 other cases (2.4%), the ITA was truncated proximally, adjacent to a sternal wire suture. In no case was atherosclerotic disease evident within the ITA.

This survey confirms the findings of Krijne et al that congenital anomalies and atherosclerotic disease of the ITA that interfere with its use in myocardial revascularization are uncommon. However, in 2.4% of patients who have undergone previous vein grafting, the left ITA may not be available as a conduit for a second operation as a result of sternotomy suture. The proportion may be higher in patients considered for third-time or subsequent operations.

Simon W. Davies, MA, MRCP
London, United Kingdom
12 September 1990

1. Krijne R, Deng M C-H K, Heinrich K-W, Sons H, Krian A. Semiselective angiography of the internal mammary arteries as a preparation for coronary bypass surgery. *Am J Cardiol* 1990;66:377–378.
2. Warwick R, Williams PL, eds. Gray's Anatomy, 35th edition. London: Longman, 1973: 644.

Antiarrhythmic Drugs and Cardiac Death End Points

I would like to offer some comments on the article by Aronow et al entitled "Effect of quinidine or procainamide versus no antiarrhythmic drug on sudden cardiac death, total cardiac death, and total death in elderly patients with heart disease and complex ventricular arrhythmias," which appeared in the August 15, 1990 issue of the *Journal*.[1]

A cursory reading of the title and abstract could erroneously suggest to the reader that procainamide was a major component of the study. In fact, only 9 of 406 patients (2.2%) in the study were treated with procainamide, and those 9 were placed on procainamide only because of a history of quinidine intolerance. Nevertheless, Aronow et al seem to give equal weight to quinidine and procainamide in their conclusions: "Data from our study showed that elderly patients developed a high incidence of adverse effects from quinidine (48%) or procainamide (55%) causing cessation of therapy."

We find the interpretation of the data gathered on procainamide to be presented in a highly skewed manner by the authors of this paper. We also hope that the methods, patient characteristics, and results of this study will be presented more clearly by the authors in future discussions and publications of their research findings.

James H. Weir, MD
Morris Plains, New Jersey
15 October 1990

1. Aronow WS, Mercando AD, Epstein S, Kronzon I. Effect of quinidine or procainamide versus no antiarrhythmic drug on sudden cardiac death, total cardiac death, and total death in elderly patients with heart disease and complex ventricular arrhythmias. *Am J Cardiol* 1990; 66:423–428.

REPLY: We agree with Dr. Weir, who is Vice President-Medical for Parke-Davis, which manufactures Procan SR®, that reading only the title of our article could lead one to believe that procainamide was a major component of our study. However, the abstract clearly states that 397 patients were treated with quinidine, and 9 with procainamide. Practicing clinicians do not alter medical management based upon the title of an article, even if the title makes a conclusionary statement (which our title does not).

Our conclusions relate to comparisons between the group of patients treated with antiarrhythmic drugs and the group that was not treated. Percentages of patients who developed adverse effects while receiving the drugs are statements of fact, not conclusions. There was a high percentage of intolerance to procainamide among our elderly patients (2 of 9 with early and 3 of 9 with late noncardiac adverse effects). In fact, 1 week after the end of the study, another patient developed a systemic lupus erythematosus-like syndrome due to procainamide, and the drug was then stopped.

The primary purpose of our study was not to determine the incidence of adverse effects from drugs, but to compare mortality between treated and untreated patients. Procainamide was used only when patients had known previous intolerance to quinidine because of gastrointestinal effects. Two of the 4 patients who tolerated procainamide in our study had sudden cardiac death.

Wilbert S. Aronow, MD
Anthony D. Mercando, MD
Stanley Epstein, MD
Itzhak Kronzon, MD
New York, New York
22 October 1990

Therapeutic Equivalency of Procainamide—A Correction

I recently reported a case of therapeutic inequivalence between a generic and proprietary form of procainamide.[1] However, further investigation into the matter revealed that the patient received an immediate release generic preparation, whereas the proprietary form was a sustained release preparation. I do not feel that these 2 forms can be directly compared and therefore the claim of therapeutic inequivalence cannot be justified. I have always felt that it is the responsibility of medical investigators to report findings that contradict their previous data as soon as they come to light.

Blair P. Grubb, MD
Toledo, Ohio
26 September 1989

1. Grubb BP. Recurrence of ventricular tachycardia following conversion from proprietary to generic procainamide. *Am J Cardiol* 1989; 63:1532–1533.

Corrections

In an editorial by Iskandrian on pages 223 and 224 of the July 15, 1990 issue, citations in the text and references misidentify the author and title of a study published in the same issue. Reference 10 should read: Hochleitner M, Hörtnagl H, Ng C-K, Hörtnagl H, Gschnitzer F, Zechmann W. Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. *Am J Cardiol* 1990;66:198–202.

In: "Prognosis and Predisposing Factors for Essential Malignant Hypertension in Predominantly Black Patients" in the October 1, 1990 issue, page 868, the authors mistakenly omitted the name of another author: Dr. Misa Hidaka.

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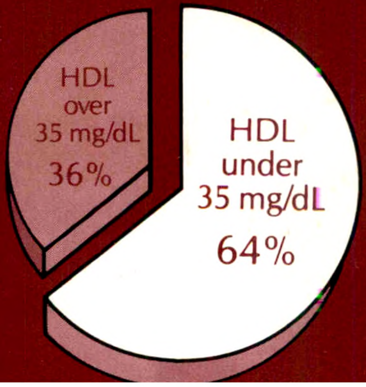

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Member, American Business Press, Inc. and Audit Bureau of Circulations. Published 3 times a month in January, April and December, 2 times in February, July and August, 4 times in March, May, June and November, and 5 times in September and October, by Cahners Publishing Company, a Division of Reed Publishing USA, 275 Washington St., Newton, MA 02158-1630. Terrence M. McDermott, President; Robert T. Brawn, Senior Vice President/General Manager; Jerry D. Neth, Senior Vice President/Publishing Operations; J.J. Walsh, Senior Vice President/Finance; Thomas J. Dellamaria, Senior Vice President/Production and Manufacturing. Executive, Editorial and Advertising Offices: 249 West 17th Street, New York, NY 10011. Printed in Easton, PA.

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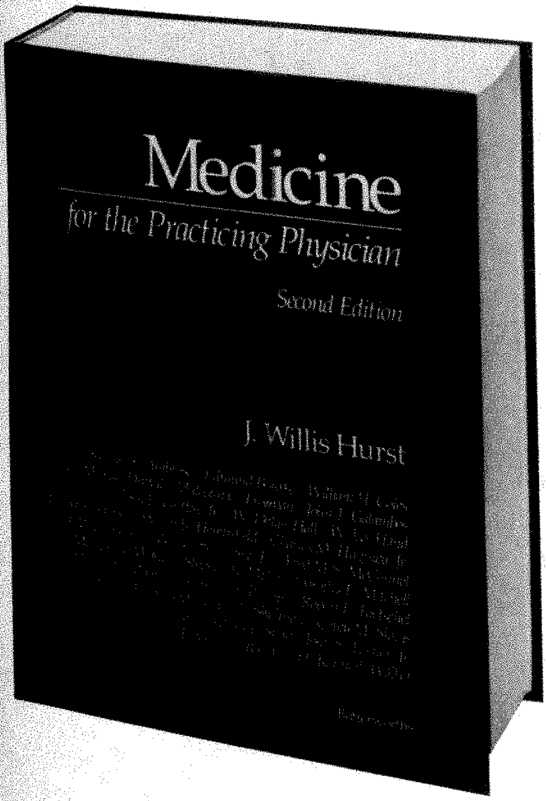

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William E. Boden, Ronald J. Krone, Robert E. Kleiger, David Oakes, Henry Greenberg, Edward J. Dwyer, Jr., J. Philip Miller, Jonathan Abrams, James Coromilas, Robert Goldstein, Arthur J. Moss, and the Multicenter Diltiazem Post-Infarction Trial Research Group

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Dynamic QRS-Complex and ST-Segment Monitoring in Acute Myocardial Infarction During Recombinant Tissue-Type Plasminogen Activator Therapy

Mikael Dellborg, Martin Riha, and Karl Swedberg, for the TEAHAT Study Group

Patients with strongly suspected acute myocardial infarction included in a placebo-controlled trial of 100 mg of recombinant tissue-type plasminogen activator were monitored for 24 hours with continuous, on-line vectorcardiography. Treatment with intravenous rt-PA limited total QRS vector change, but the QRS vector changes observed occurred more rapidly and reached a plateau earlier in patients treated with rt-PA than in those receiving placebo.

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Exercise Echocardiography and Technetium-99m MIBI Single-Photon Emission Computed Tomography in the Detection of Coronary Artery Disease

Massimo M. A. Pozzoli, Paolo M. Fioretti, Alessandro Salustri, Ambroos E. M. Reijs, and Jos R. T. C. Roelandt

To compare the relative diagnostic value of exercise echocardiography with perfusion technetium-99m metoxyisobutylisonitrile single-photon emission computed tomography in detecting coronary artery disease, 75 patients with suspected CAD but a normal electrocardiogram at rest were included in a prospective correlative study. Exercise echocardiography showed a lower sensitivity than SPECT in patients with 1-vessel disease. SPECT was tendentially more sensitive than echocardiography in detecting isolated left circumflex stenoses.

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Impaired Left Ventricular Filling and Regional Diastolic Asynchrony at Rest in Coronary Artery Disease and Relation to Exercise-Induced Myocardial Ischemia

Pasquale Perrone-Filardi, Stephen L. Bacharach, Vasken Dilsizian, and Robert O. Bonow

Of 49 patients with coronary artery disease whose left ventricular systolic function was normal at rest, 23 patients (group 2) had impaired diastolic function at rest and an abnormal ejection fraction response, as assessed by radionuclide angiography, to exercise. Among patients with CAD with normal LV systolic function at rest, impaired LV filling and diastolic asynchrony at rest reflect a greater degree of exercise-induced ischemia, suggesting a greater extent of jeopardized myocardium.

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The Dutch Experience in Percutaneous Transluminal Angioplasty of Narrowed Saphenous Veins Used for Aortocoronary Arterial Bypass

H. W. Thijs Plokker, B. Hannie Meester, and Patrick W. Serruys

We reviewed the long-term follow-up of 454 patients who underwent angioplasty of ≥1 saphenous vein bypass graft in The Netherlands between 1980 and 1988. The primary success rate was 90%. There were significant differences in event-free survival between patients who had bypass surgery 1 year before angioplasty, between 1 and 5 years, and 5 years before angioplasty, respectively. Less than one-third of patients with previous bypass surgery who underwent graft angioplasty remained event-free after 5 years. In patients needing angioplasty within 1 year after bypass surgery, better long-term results are reported.

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Predictors of Cardiac Survival After Percutaneous Transluminal Coronary Angioplasty in Patients with Severe Left Ventricular Dysfunction

Harvey Serota, Ubeydullah Deligonul, Woo-Hyeong Lee, Frank Aguirre, Morton J. Kern, Sue A. Taussig, and Michel G. Vandormael

Seventy-three patients with left ventricular ejection fraction ≤40% who underwent percutaneous transluminal coronary angioplasty were analyzed to assess the outcome of PTCA and to determine predictors of mortality. A lower LV ejection fraction, congestive heart failure, and a higher myocardial jeopardy score for contractile myocardium were independent predictors of survival after PTCA in patients with LV dysfunction. A high-risk subset can be identified among patients with severe LV dysfunction who undergo PTCA.

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Effects of Diltiazem on Complications and Restenosis After Coronary Angioplasty

James H. O'Keefe, Jr., Lee V. Giorgi, Geoffrey O. Hartzler, Thomas H. Good, Robert W. Ligon, Deborah L. Webb, and Ben D. McCallister

A total of 201 patients were randomized to either diltiazem or placebo in a double-blinded trial conducted to evaluate the usefulness of high-dose diltiazem after coronary angioplasty. Diltiazem was not effective in preventing restenosis and late cardiac events and should not be routinely used after coronary angioplasty.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Atrial Natriuretic Peptide Response to Cardioversion of Atrial Flutter and Fibrillation and Role of Associated Heart Failure

Sakti Mookherjee, Gunnar Anderson, Jr., Harold Smulyan, and Suman Vardan

Plasma atrial natriuretic peptide concentrations were measured before and 1 hour after cardioversion in 40 patients, 27 with atrial flutter and 13 with atrial fibrillation, admitted for elective cardioversion. It is concluded that (1) the ANP level is elevated comparably in patients with both atrial flutter and fibrillation regardless of the presence or absence of congestive heart failure; and (2) the level decreases, independent of the mode of cardioversion or presence of CHF, promptly after successful cardioversion.

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Sudden Cardiac Death While Wearing a Holter Monitor

Klaus V. Olshausen, Thomas Witt, Tiberius Pop, Norbert Treese, Klaus-Peter Bethge, and Jürgen Meyer

The Holter tapes of 61 patients with sudden cardiac death while being monitored were analyzed. Ventricular premature beats and complex arrhythmias increased significantly only within the last of 6 premortal hours. Monomorphic ventricular tachycardia is the arrhythmia most frequently associated with sudden cardiac death.

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Carlo Gaudio, Gaetano Tanzilli, Pietro Mazzarotto, Mario Motolese, Francesco Romeo, Benedetto Marino, and Attilio Reale

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CORONARY ARTERY DISEASE

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Electrocardiographic Subset Analysis of Diltiazem Administration on Long-Term Outcome After Acute Myocardial Infarction

William E. Boden, Ronald J. Krone, Robert E. Kleiger, David Oakes, Henry Greenberg, Edward J. Dwyer, Jr., J. Philip Miller, Jonathan Abrams, James Coromilas, Robert Goldstein, Arthur J. Moss, and the Multicenter Diltiazem Post-Infarction Trial Research Group

The effect of diltiazem on long-term outcome after acute myocardial infarction (AMI) was assessed for 2,377 patients enrolled in the Multicenter Diltiazem Post-Infarction Trial and subsequently followed for 25 ± 8 months. The study population included 855 patients (36%) with at least 1 prior AMI before the index infarction and 1,522 patients (64%) with a first AMI, of whom 409 (27%) had a first non-Q-wave AMI infarction, 664 (44%) a first inferior Q-wave AMI, and 449 (30%) a first anterior Q-wave AMI. This post hoc analysis revealed that, among patients with first non-Q-wave and first inferior Q-wave AMI, there were fewer cardiac events during follow-up in the diltiazem than in the placebo group, and that the reverse was true for patients with first anterior Q-wave AMI or prior infarction. The diltiazem:placebo Cox hazard ratio (95% confidence limits) for the trial primary end point (cardiac death or nonfatal reinfarction, whichever occurred first) was: first non-Q-wave AMI—0.48 (0.26, 0.89); first inferior Q-wave AMI—0.66 (0.40, 1.09); first anterior Q-wave AMI—0.82 (0.51, 1.31); and prior AMI—1.11 (0.85, 1.44). Use of cardiac death alone as an end point gave an even more sharply focused treatment difference: first non-Q-wave AMI—0.46 (0.18, 1.21); first inferior Q-wave AMI—0.53 (0.27, 1.06); first anterior Q-wave AMI—1.28 (0.68, 2.40); and prior infarction—1.26 (0.90, 1.77). The differential effect of diltiazem on postinfarction outcome in these electrocardiographically categorized AMI subsets appears closely linked to the bidirectional effect of diltiazem (beneficial in most patients with well-preserved left ventricular function, and harmful in the minority with impaired left ventricular function) that was elucidated in the primary Multicenter Diltiazem Post-Infarction Trial analysis. In patients with multiple infarctions complicated by left ventricular dysfunction, diltiazem appears to be detrimental. Patients with first non-Q-wave or first inferior Q-wave infarction generally have well-preserved left ventricular function and appear to benefit from diltiazem.

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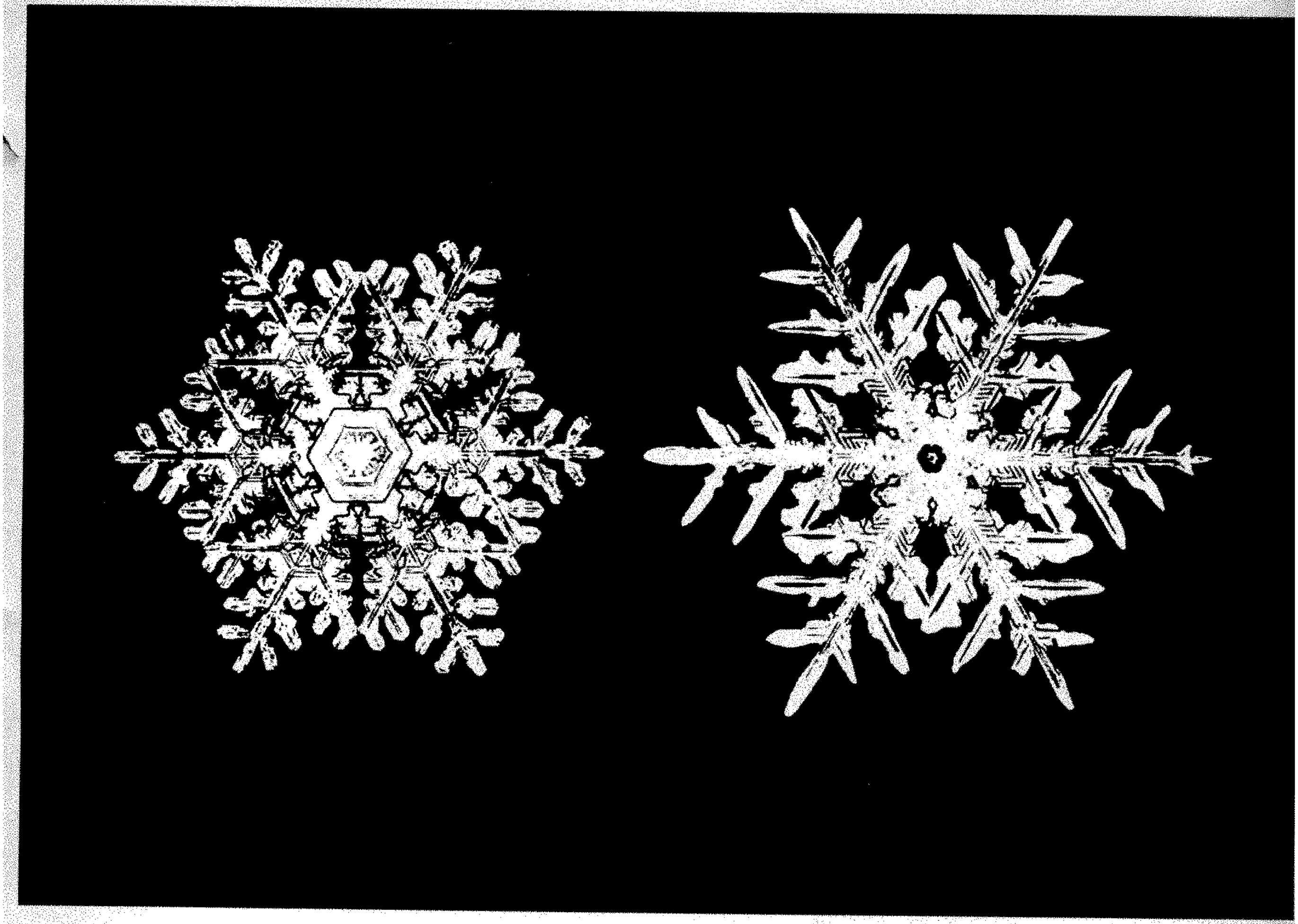

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Dynamic QRS-Complex and ST-Segment Monitoring in Acute Myocardial Infarction During Recombinant Tissue-Type Plasminogen Activator Therapy

Mikael Dellborg, Martin Riha, and Karl Swedberg, for the TEAHAT Study Group

A more rapid development of QRS changes has been reported in patients treated with thrombolytic agents. Patients with strongly suspected acute myocardial infarction included in a placebo-controlled trial of 100 mg of recombinant tissue-type plasminogen activator (rt-PA) were monitored for 24 hours with continuous, on-line vectorcardiography. The magnitude of the QRS vector changes correlated with infarct size estimated by the maximal value of lactate dehydrogenase–1 ($r = 0.69$, $p < 0.001$) as well as with left ventricular ejection fraction 30 days after randomization ($r = 0.49$, $p < 0.001$). Treatment with intravenous rt-PA limited total QRS vector change but the QRS vector changes observed occured more rapidly and reached a plateau 131 minutes earlier in patients treated with rt-PA than in the placebo group ($p < 0.01$). A certain pattern of highly variable ST vector magnitude was associated with higher maximal lactate dehydrogenase–1 values and a tendency to higher 1-year mortality.

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Exercise Echocardiography and Technetium-99m MIBI Single-Photon Emission Computed Tomography in the Detection of Coronary Artery Disease

Massimo M. A. Pozzoli, Paolo M. Fioretti, Alessandro Salustri, Ambroos E. M. Reijs, and Jos R. T. C. Roelandt

Exercise echocardiography and perfusion technetium-99m metoxyisobutylisonitrile single-photon emission computed tomography (SPECT) were simultaneously performed in 75 patients with suspected coronary artery disease and a normal electrocardiogram at rest; new wall motion abnormalities or transient perfusion defects, or both, were considered as a positive test and the results were compared with coronary angiography. The overall sensitivities and specificities were 71 and 96% for echocardiography and 84 and 88% for SPECT; the agreement between the 2 methods was 88%. Exercise echocardiography showed a lower sensitivity than SPECT in patients with 1-vessel disease (61 vs 82%, $p < 0.02$). SPECT was tendentially more sensitive than echocardiography in detecting isolated left circumflex stenoses.

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Impaired Left Ventricular Filling and Regional Diastolic Asynchrony at Rest in Coronary Artery Disease and Relation to Exercise-Induced Myocardial Ischemia

Pasquale Perrone-Filardi, Stephen L. Bacharach, Vasken Dilsizian, and Robert O. Bonow

To assess whether impaired left ventricular (LV) diastolic function at rest in patients with coronary artery disease (CAD) reflects the functional severity of CAD, as estimated by exercise-induced ischemia, we performed radionuclide angiography in 49 patients with normal LV systolic

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function at rest. Group 1 patients (n = 26) had a normal ejection fraction response to exercise and group 2 patients (n = 23) an abnormal response. Data obtained from 22 age-comparable normal volunteers were used for comparison. Peak filling rate was lower in group 2 patients than in normal subjects (2.5 ± 0.8 vs 3.2 ± 0.6 end-diastolic counts/s; $p <0.01$). Moreover, diastolic asynchrony at rest was greater in group 2 patients (46 ± 44 ms) than in both normal subjects (25 ± 16 ms; $p <0.05$) and group 1 patients (23 ± 16 ms; $p <0.05$). Thus, among patients with CAD and normal LV systolic function at rest, impaired LV filling and diastolic asynchrony at rest reflect a greater degree of exercise-induced ischemia, suggesting a greater extent of jeopardized myocardium.

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The Dutch Experience in Percutaneous Transluminal Angioplasty of Narrowed Saphenous Veins Used for Aortocoronary Arterial Bypass

H. W. Thijs Plokker, B. Hannie Meester, and Patrick W. Serruys

Long-term follow-up of 454 patients who underwent an angioplasty of single or sequential saphenous vein bypass grafts in The Netherlands between 1980 and 1988 was studied. The primary success rate was 90%. In-hospital mortality was 0.7%, 2.8% of patients sustained a procedural myocardial infarction, and 1.3% of patients had to undergo emergency bypass surgery. After 5 years 74% of patients were alive, and 26% of patients were alive and event-free. Only 3% of patients who underwent an unsuccessful angioplasty were event-free at 5 years, versus 27% in successfully dilated patients. There were significant differences in event-free survival between patients who had bypass surgery 1 year before angioplasty, between 1 and 5 years, and 5 years before angioplasty, respectively. Less than one-third of patients with previous bypass surgery who underwent graft angioplasty remained event-free after 5 years. In patients needing angioplasty within 1 year after bypass surgery, better long-term results are reported.

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Predictors of Cardiac Survival After Percutaneous Transluminal Coronary Angioplasty in Patients with Severe Left Ventricular Dysfunction

Harvey Serota, Ubeydullah Deligonul, Woo-Hyeong Lee, Frank Aguirre, Morton J. Kern, Sue A. Taussig, and Michel G. Vandormael

To assess the outcome of percutaneous transluminal coronary angioplasty (PTCA) in patients with severe left ventricular (LV) dysfunction and to determine the predictors of mortality, 73 patients with LV ejection fraction $\geq$40% who underwent initial PTCA were analyzed. The majority of patients had prior myocardial infarction. Multivessel coronary artery disease was present in 83%. Intraaortic balloon pump (15%) and percutaneous cardiopulmonary bypass support (4%) was used infrequently. Angiographic success was obtained in 109 of 128 lesions (85%) attempted. The procedural mortality was 5%. All patients were followed up for $\geq$6 to 71 months. The estimated survival was 79% ± 5, 74% ± 6, 66% ± 7 and 57% ± 8 at 1, 2, 3 and 4 years, respectively. A Cox regresssion analysis revealed that the presence of congestive heart failure, a lower ejection fraction and a higher myocardial jeopardy score were independent predictors of survival after PTCA in patients with LV dysfunction.

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Effects of Diltiazem on Complications and Restenosis After Coronary Angioplasty

James H. O'Keefe, Jr., Lee V. Giorgi, Geoffrey O. Hartzler, Thomas H. Good, Robert W. Ligon, Deborah L. Webb, and Ben D. McCallister

A randomized, placebo-controlled, double-blinded trial was conducted to evaluate the effectiveness of high-dose diltiazem in the prevention of cardiac events and restenosis in patients after coronary angioplasty. A total of 201 patients were randomized to diltiazem or placebo. Treatment began 24 hours before angioplasty. The incidence of late cardiac events (recurrent angina, death, Q-wave infarction or coronary artery bypass graft surgery) was similar in the 2 treatment groups. Restenosis was evaluated by quantitative angiographic techniques, and 60% of patients were restudied at 1 year. The restenosis rates were 36% in the diltiazem and 32% in the placebo groups ($p = 0.30$). Thus, diltiazem was ineffective in preventing restenosis and late cardiac events after coronary angioplasty and should be reserved for patients with a specific indication for the drug.

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Atrial Natriuretic Peptide Response to Cardioversion of Atrial Flutter and Fibrillation and Role of Associated Heart Failure

Sakti Mookherjee, Gunnar Anderson, Jr., Harold Smulyan, and Suman Vardan

Plasma atrial natriuretic peptide (ANP) levels were measured before and 1 hour after elective cardioversion in 27 patients with atrial flutter and 13 with atrial fibrillation. One patient had spontaneous and 2 pharmacologic cardioversion, whereas the remaining 37 needed electrical cardioversion, which was successful in 36 patients. Congestive heart failure was observed in 14 patients (11 with atrial flutter and 3 with atrial fibrillation). Independent of the congestive heart failure status, duration of arrhythmia or left atrial size, the ANP levels that were elevated comparably in patients with atrial flutter and fibrillation decreased significantly after cardioversion. Use of anesthesia for electrical cardioversion or the mode of cardioversion did not influence the ANP response to conversion to sinus rhythm. The patient in whom cardioversion was unsuccessful had an unchanged, elevated ANP level. The change in ANP after cardioversion correlated strongly with its pretreatment level but not with the change in ventricular rate or blood pressure.

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Sudden Cardiac Death While Wearing a Holter Monitor

Klaus V. Olshausen, Thomas Witt, Tiberius Pop, Norbert Treese, Klaus-Peter Bethge, and Jürgen Meyer

The Holter tapes of 61 patients with sudden cardiac death while being monitored were analyzed. In the premortal hours, repetitive ventricular arrhythmias were found in 50 patients (82%), with atrial fibrillation in 34%. Patients with bradyarrhythmic death (18%) had less ventricular

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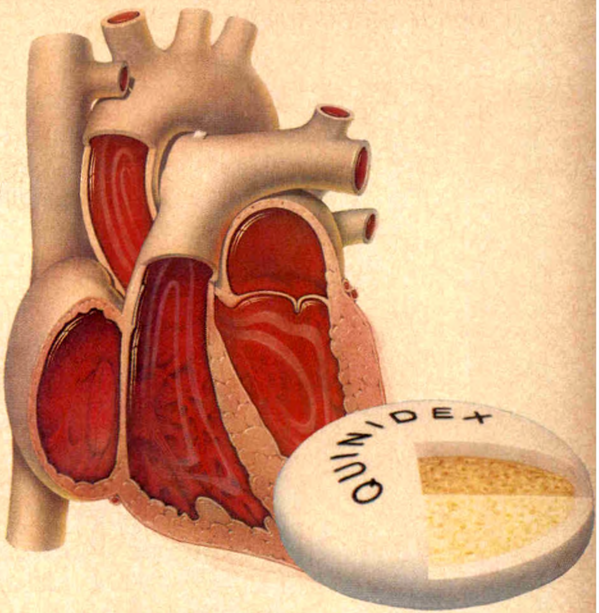

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Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	**Effect**
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital), phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

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ectopic activity than did patients with tachyarrhythmic death (82%, p <0.01). Monomorphic ventricular tachycardia was found in 26 patients (43%), polymorphic tachycardia in 15 (25%), torsades de pointes in 5 (8%), primary ventricular fibrillation in 3 (5%) and atrial tachycardia in 1 patient. In tachyarrhythmic patients, an increase in heart rate within the last 3 hours was noted (83 vs 89 beats/min, p <0.05). Ventricular premature beats and complex arrhythmias increased significantly only within the last hour. Thus, monomorphic ventricular tachycardia is the arrhythmia most frequently associated with sudden death. Increase in heart rate before death is small and clinically insignificant. Increase in complex ectopy is noticed only within the last hour.

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Late Results of the Left Subcostal Approach for Automatic Implantable Cardioverter Defibrillator Implantation

Padraig G. O'Neill, Gerald M. Lawrie, Raj R. Kaushik, Lynette F. Harvill, and Antonio Pacifico

This study evaluated the late results of the left subcostal surgical approach for the implantation of an automatic implantable cardioverter defibrillator (AICD) in 48 consecutive patients with life-threatening ventricular arrhythmias. Patients were followed for a minimum of 1 year. Satisfactory intraoperative defibrillation thresholds were obtained in 42 patients. The mean intraoperative defibrillation threshold for the entire group was 13.8 ± 6.6 J. Minimal surgical morbidity was noted and postoperative convalescence was rapid. Long-term survival and freedom from arrhythmic death was comparable to that achieved with other surgical techniques. The subcostal approach for AICD implantation is the procedure of choice unless concomitant open-heart surgery is planned.

CONGESTIVE HEART FAILURE

391

Influence of Dilated Cardiomyopathy, Myocarditis and Cardiac Transplantation on the Relation Between Plasma Atrial Natriuretic Factor and Atrial Pressures

Joshua M. Hare, Kenneth L. Baughman, David A. Kass, Steven N. Goodman, and Paul W. Ladenson

To test whether dilated cardiomyopathy, myocarditis or cardiac transplantation affect the relation between atrial natriuretic factor (ANF) level and filling pressures, right atrial plasma ANF concentration, pulmonary arterial wedge pressure and right atrial pressure were measured in patients with dilated cardiomyopathy with and without myocarditis and in patients with prior cardiac transplantation. ANF was significantly correlated with pulmonary arterial wedge and right atrial pressures in cardiomyopathy patients both with and without myocarditis. However, myocarditis was not a significant independent predictor of ANF level. A significant number of cardiomyopathy patients with normal filling pressures had elevated circulating ANF. Cardiac transplant recipients displayed no correlation between ANF level and either right or left filling pressures. In conclusion, left and right atrial pressures are important determinants of circulating

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ANF level unaffected by inflammation in most patients with cardiomyopathy, whereas other factors influence plasma ANF concentrations in a significant number of patients with cardiomyopathy and in denervated human hearts.

VALVULAR HEART DISEASE

398

Beneficial Effect of Atrial Pacing in Severe Acute Aortic Regurgitation and Role of M-Mode Echocardiography in Determining the Optimal Pacing Interval

Theo E. Meyer, Pinhas Sareli, Richard H. Marcus, Jai Patel, and Martin R. Berk

The effect of atrial pacing on the hemodynamics of acute, severe aortic regurgitation was assessed in 11 patients, all of whom had diastolic closure of the mitral valve. Once baseline recordings were obtained, the pacing rate was increased by 10 beats/min to a maximal rate of 140 beats/min. The optimal pacing interval was defined as that at which the lowest filling pressure was associated with the highest cardiac output. This interval was then compared with a pacing interval derived from the R wave of the electrocardiogram to the mitral closing point on the echocardiogram. The optimal rate ranged from 110 to 130 beats/min (mean 120 ± 8), and differed from the echocardiographic-derived pacing interval by 18 ± 21 ms. At the optimal rate, left ventricular end-diastolic pressures decreased from 46 ± 7 to 23 ± 12 mm Hg ($p < 0.001$), and the pulmonary arterial wedge pressures from 28 ± 8 to 16 ± 7 mm Hg ($p < 0.001$), while the cardiac index increased from 2.34 ± 0.46 to 2.63 ± 0.49 liters/min/m^2 ($p < 0.01$). Atrial pacing has a predictable, beneficial effect in acute, severe aortic regurgitation. The optimal rate can be predetermined from the echocardiogram.

CARDIOMYOPATHY

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Simultaneous Occurrence of Mitral Valve Prolapse and Systolic Anterior Motion in Hypertrophic Cardiomyopathy

Julio A. Panza and Barry J. Maron

This report describes a subset of patients with hypertrophic cardiomyopathy (HC) and unusual mitral valve dynamics involving systolic anterior motion (SAM) and marked mitral valve prolapse (MVP). By echocardiography, the mitral valve in these patients appeared to be increased in size relative to the left ventricular cavity and mitral anulus. Distal portions of the mitral leaflets approached or made contact with the ventricular septum, while the proximal portion of the leaflets showed marked excursion into the left atrium. Three mitral valves available for gross visual inspection did not show the morphologic features of primary MVP. Clinical and morphologic findings did not differ from those in the overall population of patients with HC. Such patients further define the great diversity evident

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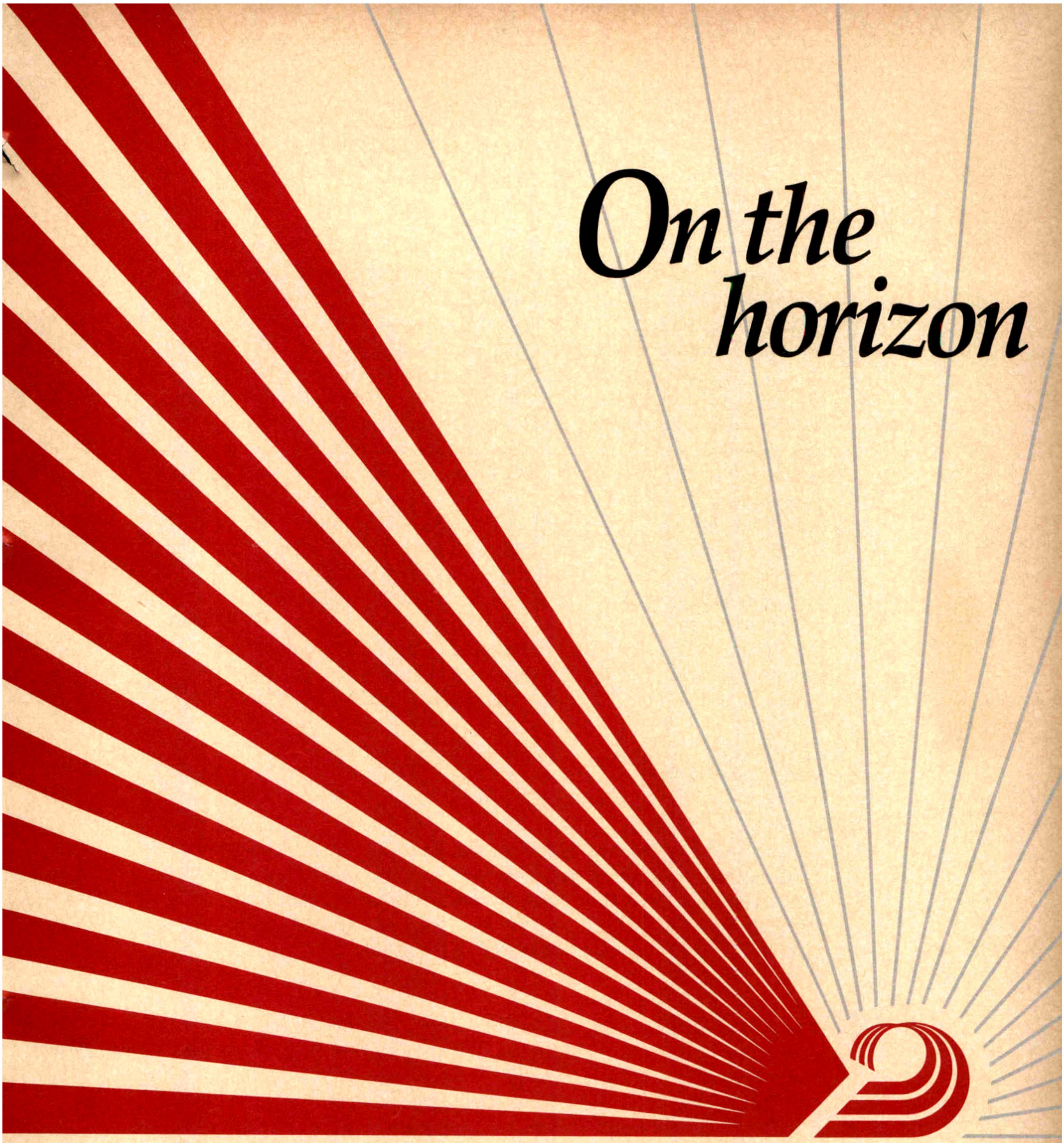

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within the clinical spectrum of HC and emphasize that functional abnormalities in this disease are not confined to left ventricular myocardium but also involve the mitral valve.

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Comparison of Left Ventricular Ejection Fraction by Magnetic Resonance Imaging and Radionuclide Ventriculography in Idiopathic Dilated Cardiomyopathy

Carlo Gaudio, Gaetano Tanzilli, Pietro Mazzarotto, Mario Motolese, Francesco Romeo, Benedetto Marino, and Attilio Reale

Left ventricular ejection fraction determined by spin-echo multislice-multiphase gated magnetic resonance imaging (MRI) on the short-axis plane was compared with equilibrium radionuclide ventriculography in 32 patients with idiopathic dilated cardiomyopathy. The 2 examinations were consecutively performed in our center on the same day, with a mean time interval of 40 minutes. A high correlation was obtained ($y = 0.79 \times +3.51$, $r = 0.91$; $p < 0.001$) and a good agreement between measurements of the 2 methods (mean difference 1.7, with 95% confidence interval 0.71 to 2.68). MRI interobserver and intrapatient variability also showed a high correlation ($r = 0.91$, $r = 0.98$). Our data suggest that MRI, using the short-axis approach and the multislice-multiphase technique, is an accurate, noninvasive, reproducible method for determining left ventricular ejection fraction in patients with idiopathic dilated cardiomyopathy.

MISCELLANEOUS

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Stroke Volume During Submaximal Exercise in Endurance-Trained Normotensive Subjects and in Untrained Hypertensive Subjects with Beta Blockade (Propranolol and Pindolol)

Kathy D. Scruggs, Nicholaus B. Martin, Craig E. Broeder, Zandrie Hofman, Evan L. Thomas, Kathleen C. Wambsgans, and Jack H. Wilmore

The effect of β-adrenergic blockade on stroke volume (SV) at increasing submaximal exercise intensities was studied in 12 endurance-trained normotensive and 12 untrained hypertensive (diastolic blood pressure >95 mm Hg) men, aged 18 to 34 years, while assigned to each of 3 treatments: placebo, propranolol and pindolol. Cardiac outputs were estimated at rest and while walking on a treadmill at 25, 45, 60 and 75% of the subject's previously determined maximal oxygen uptake. No significant differences were found in cardiac output between either of the drugs and placebo at rest, or at any of the 4 rates of work. Propranolol significantly increased SV above placebo values ($p < 0.05$) for both trained and untrained subjects at the intensities of 45, 60 and 75%. Significant differences in SV were found between pindolol and placebo only at the intensities of 60 and 75% in the trained men.

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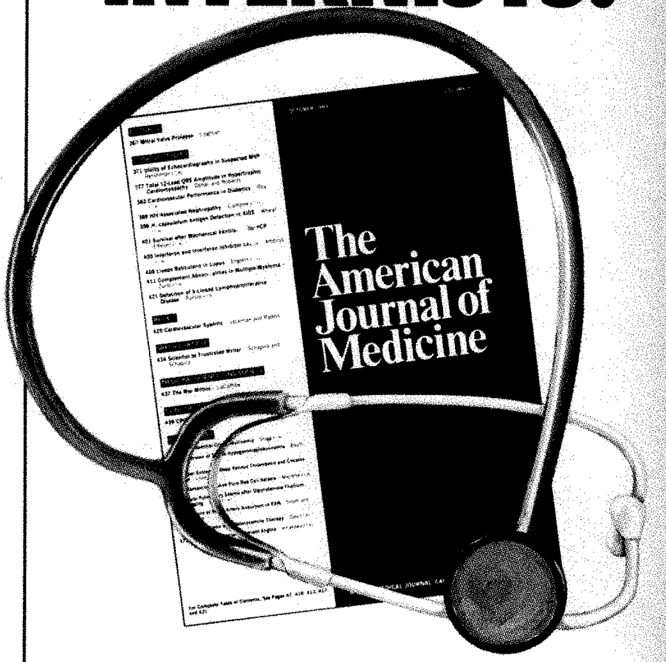

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

FEBRUARY 15, 1991, VOL. 67, NO. 5

Electrocardiographic Subset Analysis of Diltiazem Administration on Long-Term Outcome After Acute Myocardial Infarction

William E. Boden, MD, Ronald J. Krone, MD, Robert E. Kleiger, MD, David Oakes, PhD, Henry Greenberg, MD, Edward J. Dwyer, Jr, MD, J. Philip Miller, MS, Jonathan Abrams, MD, James Coromilas, MD, Robert Goldstein, MD, Arthur J. Moss, MD, and the Multicenter Diltiazem Post-Infarction Trial Research Group

The effect of diltiazem on long-term outcome after acute myocardial infarction (AMI) was assessed in 2,377 patients enrolled in the Multicenter Diltiazem Post-Infarction Trial and subsequently followed for 25 ± 8 months. The study population included 855 patients (36%) with at least 1 prior AMI before the index infarction and 1,522 patients (64%) with a first AMI, of whom 409 (27%) had a first non-Q-wave AMI, 664 (44%) a first inferior Q-wave AMI, and 449 (30%) a first anterior Q-wave AMI. This post hoc analysis revealed that, among patients with first non-Q-wave and first inferior Q-wave AMI, there were fewer cardiac events during follow-up in the diltiazem than in the placebo group, and that the reverse was true for patients with first anterior Q-wave AMI or prior infarction. The diltiazem:placebo Cox hazard ratio (95% confidence limits) for the trial primary end point (cardiac death or nonfatal reinfarction, whichever occurred first) was: first non-Q-wave AMI—0.48 (0.26, 0.89); first inferior Q-wave AMI—0.66 (0.40, 1.09); first anterior Q-wave AMI—0.82 (0.51, 1.31); and prior AMI—1.11 (0.85, 1.44). Use of cardiac death alone as an end point gave an even more sharply focused treatment difference: first non-Q-wave AMI—0.46 (0.18, 1.21); first inferior Q-wave AMI—0.53 (0.27, 1.06); first anterior Q-wave AMI—1.28 (0.68, 2.40); prior infarction—1.26 (0.90, 1.77).

Further analysis revealed that these differences in the effect of diltiazem in large part reflected the different status of the 4 electrocardiographically defined subsets in terms of left ventricular function. Mean (± standard deviation) ejection fraction for patients with first non-Q-wave AMI (placebo, 0.53 ± 0.13; diltiazem, 0.54 ± 0.12) was comparable to that of patients with a first inferior Q-wave AMI (placebo, 0.52 ± 0.10; diltiazem, 0.52 ± 0.11), and both these first AMI subsets had a lower frequency of radiographic pulmonary congestion range (10 to 16%) during the acute infarction than did patients with first anterior Q-wave or prior AMI. Mean ejection fraction for the subset of patients with first anterior Q-wave AMI (placebo, 0.38 ± 0.13; diltiazem, 0.40 ± 0.12) was comparable to that of patients with at least 1 prior AMI (placebo, 0.44 ± 0.15; diltiazem, 0.43 ± 0.14) and the frequency of pulmonary congestion in these 2 infarct subsets ranged from 24 to 26%.

The differential effect of diltiazem on postinfarction outcome in these electrocardiographically categorized AMI subsets appears closely linked to the bidirectional effect of diltiazem (beneficial in the majority of patients with well-preserved left ventricular function, harmful in the minority with impaired left ventricular function) that was elucidated in the primary Multicenter Diltiazem Post-Infarction Trial analysis. In patients with multiple infarctions complicated by left ventricular dysfunction, diltiazem appears to be detrimental. Patients with first non-Q-wave or first inferior Q-wave infarction generally have well-preserved left ventricular function and appear to benefit from diltiazem.

(Am J Cardiol 1991;67:335–342)

From the Cardiology Section, Medical Service, Veterans Administration Medical Center and Tufts University School of Medicine, Boston, Massachusetts; the Division of Cardiology, Department of Medicine, and the Department of Biostatistics, The Jewish Hospital at Washington University School of Medicine, St. Louis, Missouri; the Division of Cardiology, Department of Medicine, St. Luke's/Roosevelt Hospital and Columbia University School of Physicians and Surgeons, New York, New York; Cardiology Section, University of New Mexico, Albuquerque, New Mexico; Cardiology Division, Department of Medicine, United States Public Health Service Medical Center, Bethesda, Maryland; Heart Research Follow-Up Program and Division of Biostatistics, University of Rochester Medical Center, Rochester, New York. This study was supported by a consortium grant from Godecke Aktiengesellschaft (Germany); Laboratorios Dr. S.A. Esteve (Spain); Marion Laboratories Inc. (USA); Nordic Laboratories, Ltd. (Canada); Lars Synthelabo (France); Tanabe Seiyaku Co., Ltd. (Japan); Warner-Lambert International, Inc. (USA). Manuscript received July 13, 1990; revised manuscript received October 3, 1990, and accepted October 5.

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A major determinant of outcome after acute myocardial infarction (AMI) is the extent of mechanical damage to left ventricular function.[1-3] Severity of left ventricular dysfunction is determined, in part, by the presence of prior infarction, by the electrocardiographic type (Q-wave versus non-Q-wave), and by the location (anterior versus inferior) of infarction.[4-7] For example, patients with a first non-Q-wave AMI generally have a more favorable long-term prognosis than patients with extensive, or recurrent, Q-wave infarction.[6,7]

The primary report from the Multicenter Diltiazem Post-Infarction Trial (MDPIT), published in 1988,[8] showed that diltiazem exerted no overall salutary effect on long-term cardiac death or recurrent infarction. However, when patients were subgrouped according to the presence or absence of radiographic pulmonary congestion during the index hospitalization, a significant bidirectional (harmful or beneficial) diltiazem effect was observed in those patients who did or did not manifest radiographic pulmonary congestion, respectively, during the acute infarct event.[8] This detailed covariate analysis of the MDPIT indicated that there was a diltiazem-related reduction in cardiac death in patients after infarction with well-preserved left ventricular function, and a diltiazem-related increase in cardiac death in patients with impaired ventricular function.[9]

In the earlier Diltiazem Reinfarction Study, prophylactic diltiazem administration for up to 14 days after acute non-Q-wave AMI was associated with a significant reduction in early reinfarction, although the 2-week mortality rate was similar in the diltiazem and placebo-treated groups.[10] Accordingly, because the Diltiazem Reinfarction Study emphasized the beneficial short-term efficacy of diltiazem in a single electrocardiographically defined AMI subset, the purpose of the present study was to assess the effect of diltiazem on long-term outcome in several electrocardiographically categorized AMI subsets, using the extensive MDPIT database. In particular, a new electrocardiographic analysis code was designed for the MDPIT study[11]; it was tested by retrospective application to the previously published Multicenter Post-Infarction Program,[1] and was subsequently validated in a large, prospective, post-infarction clinical trial.[10,12] For the present study, the relations among the electrocardiographic subtype (Q-wave versus non-Q-wave), site (anterior versus inferior), and underlying state of left ventricular function were examined systematically to clarify further the effect of diltiazem in various subsets of patients recovering from AMI, and to provide therapeutic guidelines for the optimal use of diltiazem in patients after infarction.

METHODS

The design, organization, patient recruitment, data acquisition, follow-up and data management aspects of MDPIT have been reported previously.[8,9] The analyses used the analytic database released April 16, 1988.

Study population: The original MDPIT study population included 2,466 patients (1,234 assigned to placebo, 1,232 to diltiazem). Overall, 19% of the 13,618 eligible post-AMI patients who met study inclusion criteria were enrolled in the trial. Patients were excluded for various clinical and logistic reasons, as previously reported.[8] In particular, patients were excluded if they exhibited unstable angina after AMI that required calcium antagonist therapy for control, or if coronary bypass surgery was planned. All patients enrolled in the MDPIT had enzymatic evidence of AMI, determined by the clinical laboratories at the 38 U.S. and Canadian enrolling sites, as previously detailed.[8]

Electrocardiographic classification: For the present analysis, patients with left or right bundle branch block or pacemaker rhythm on the initial qualifying electrocardiogram were excluded (n = 89). Patients with a clinical history or electrocardiographic evidence of Q-wave myocardial infarction before the index were categorized as having a prior infarction (n = 855).

The remaining patients were categorized as having a first infarction (n = 1,522), and these were further subdivided by infarct subtype (Q-wave versus non-Q-wave) and Q-wave location, according to the electrocardiographic code[11] developed for this study, and applied retrospectively to the Multicenter Post-Infarction Program.[1] Non-Q-wave AMI (n = 409) was defined by the absence of diagnostic (≥ 0.04 second) Q waves or changes of a true posterior infarction (R/S ratio ≥ 1 in lead V_2). Inferior Q-wave AMI (n = 664) was defined by the presence of diagnostic Q waves in diaphragmatic leads II, III, aVF or an R/S ratio ≥ 1 in lead V_2, or both. Anterior Q-wave AMI (n = 449) was defined as diagnostic Q waves in leads V_1-V_4 with or without Q waves in leads I, aVL, V_5 or V_6.

Left ventricular function: Two independent measures of left ventricular function were assessed in the MDPIT patients. The 2 covariates (radiographic pulmonary congestion and radionuclide ejection fraction) were among 12 variables that were prespecified before trial unblinding, using the findings from a prior post-infarction study.[1] Radiographic pulmonary congestion was defined from the most representative chest roentgenogram obtained during the initial 24- to 48-hour period of hospitalization in the coronary care unit. The presence of pulmonary congestion was assessed by the attending radiologist's interpretation at each participating institution and, for the purpose of this analysis, was defined as a dichotomous variable (none versus any congestion on the chest x-ray).[8]

Radionuclide ventriculography was performed at each enrolling site using either the first-pass or equilibrium multigated approach. Ejection fraction data were obtained using standard volume and count-based techniques, and radionuclide studies were generally obtained before hospital discharge, but not contemporaneously with the determination of radiographic pulmonary congestion by chest x-ray.

End points: The primary end point for the MDPIT was first recurrent cardiac events (cardiac death or nonfatal reinfarction, whichever occurred first during the follow-up period), as previously defined.[8,9] For this analysis, the primary end point and cardiac death alone were used to assess outcome.

TABLE I Baseline Characteristics of Electrocardiographic Subsets by Treatment Assignment

	Electrocardiographic Subsets[*]			
Characteristics	First Non-Q (n = 409)	First Inferior Q (n = 664)	First Anterior Q (n = 449)	Prior Infarct (n = 855)
Mean age (yr)				
Placebo	58 ± 9	57 ± 11	57 ± 11	59 ± 9
Diltiazem	57 ± 10	58 ± 10	56 ± 11	59 ± 10
Sex (M/F)				
Placebo	74/26	77/23	85/15	79/21
Diltiazem	74/26	80/20	80/20	85/15
Cardiac history				
NYHA class II–IV[†]				
Placebo	13	10	11	32
Diltiazem	15	14	10	29
Treatment for hypertension				
Placebo	38	32	35	45
Diltiazem	42	37	38	37
Coronary bypass surgery				
Placebo	3	2	3	11
Diltiazem	4	2	1	13
Insulin-dependent diabetes				
Placebo	7	5	8	13
Diltiazem	8	9	10	9
Cigarette smoking				
Placebo	49.3	54.0	47.6	46.6
Diltiazem	54.4	56.7	46.2	45.1
Cardiac findings				
Shock before enrollment				
Placebo	1.3	4.6	2.6	1.9
Diltiazem	3.8	3.8	0.9	2.1
Greater than bibasilar pulmonary rales				
Placebo	2.7	6.1	6.2	8.0
Diltiazem	4.3	3.9	5.0	8.9
Creatine kinase >1,000 U				
Placebo	21.9	61.7	71.4	40.7
Diltiazem	24.9	58.3	69.8	41.2
Blood urea nitrogen >35 mg/dl				
Placebo	6.7	6.8	4.8	9.6
Diltiazem	5.4	3.0	6.4	9.2
Systolic blood pressure <100 mm Hg				
Placebo	2.7	6.1	3.5	3.4
Diltiazem	3.8	6.5	1.4	3.7
Chest x-ray				
Pulmonary congestion[‡]				
Placebo	16.1	13.4	25.7	25.1
Diltiazem	10.1	14.8	24.3	25.7
Mean radionuclide ejection fraction				
Placebo	0.53 ± 0.13	0.52 ± 0.10	0.38 ± 0.13	0.44 ± 0.15
Diltiazem	0.54 ± 0.12	0.52 ± 0.11	0.40 ± 0.12	0.43 ± 0.14
Ambulatory electrocardiogram				
Mean heart rate (beats/min)				
Placebo	69 ± 12	71 ± 10	75 ± 14	74 ± 14
Diltiazem	68 ± 10	70 ± 11	71 ± 12	72 ± 13
Any ventricular ectopics				
Placebo	89.0	84.0	85.6	91.3
Diltiazem	84.1	81.7	86.7	91.6
≥10 ventricular ectopics/hour				
Placebo	14.1	13.6	14.4	22.6
Diltiazem	12.8	10.0	14.3	21.9
≥3 ventricular ectopics in a row				
Placebo	9.4	6.3	7.9	12.6
Diltiazem	13.4	4.3	11.7	15.7
Medication				
Antiarrhythmic agents				
Placebo	6.7	7.1	10.1	12.7
Diltiazem	7.0	5.9	7.7	10.5
β blockers				
Placebo	60.7	50.9	47.1	54.8
Diltiazem	67.0	54.1	56.3	52.4
Digitalis				
Placebo	10.3	6.4	22.0	17.8
Diltiazem	6.5	5.2	16.7	18.9
Diuretic agents				
Placebo	20.5	14.7	22.5	32.0
Diltiazem	19.5	15.1	21.2	29.6
Nitrates other than sublingual				
Placebo	68.3	53.1	63.4	65.6
Diltiazem	64.3	52.1	56.8	61.0

[*] Figures are percentages unless otherwise indicated; values are mean ± standard deviation.

[†] New York Heart Association functional classification 1 month before entry.

[‡] Pulmonary congestion by x-ray examination categorized as mild, moderate or severe.

Statistical analyses: Patients were assigned randomly to receive either 60 mg of diltiazem orally every 6 hours or placebo in a double-blind manner 3 to 15 days after onset while still hospitalized.[9] The randomization procedure included blocking within each hospital for the number of days from AMI onset to randomization (≤5 days, >5 days), current β-blocker usage (no, yes), and New York Heart Association functional classification 1 month before hospitalization (I vs II to IV). The study patients were followed for ≥12 months up to a maximum of 52 months; the average follow-up was 25 ± 8 months per patient. The statistical procedures used life-table methods to account for variable length of follow-up.[13] The analyses used the Cox proportional-hazards regression model[14] (BMDP-2L computer program[15]).

Patients were divided into 4 categories based on the index infarct: first non-Q-wave AMI, first inferior Q-wave AMI, first anterior Q-wave AMI and prior AMI. The individual participating hospitals were entered as stratification factors; the 3 blocking variables, 3 indicator variables representing the 4 AMI categories, and 4 indicator variables representing the treatment effect within the individual infarct categories were also included in the model. The comparison of end point events between the 2 treatment subgroups of each infarct category is reported in terms of the Cox hazard ratio. This ratio is the risk of experiencing the end point event per unit of time for patients randomized to dilitazem, to the risk for patients randomized to placebo. Separate analyses were performed for subgroups with and without radiographic pulmonary congestion and for the subgroup with radionuclide ejection fraction dichotomized at ≥0.40 or <0.40. Each of these covariates was assessed during the index hospitalization for the acute AMI.

All outcome analyses were based on the treatment group to which the patient had been randomized, i.e., the intention to treat principle. Patients who were lost to follow-up (2.3% of the enrolled population) and those who died of noncardiac causes were censored as of the date they were last known to be alive.

TABLE II Cardiac Event Rates for the Entire Follow-Up Period by Electrocardiographic Classification, Pulmonary Congestion and Treatment Assignment

Electrocardiographic Classification	Total Population Placebo (%)	Total Population Diltiazem (%)	No Pulmonary Congestion Placebo (%)	No Pulmonary Congestion Diltiazem (%)	Pulmonary Congestion Placebo (%)	Pulmonary Congestion Diltiazem (%)
Cardiac Death						
First non-Q AMI	7.0	3.0	6.0	4.0	11.0	0
First inferior Q AMI	7.0	4.0	6.0	2.0	14.0	14.0
First anterior Q AMI	9.0	9.0	6.0	6.0	18.0	21.0
Previous AMI	15.0	18.0	14.0	12.0	18.0	37.0
First Recurrent Cardiac Event						
First non-Q AMI	15.0	8.0	14.0	9.0	20.0	6.0
First inferior Q AMI	12.0	9.0	11.0	7.0	16.0	16.0
First anterior Q AMI	18.0	14.0	16.0	10.0	23.0	27.0
Previous AMI	25.0	27.0	22.0	21.0	31.0	44.0

AMI = acute myocardial infarction.

Results of continuous variables are reported as mean ± standard deviation, and all comparative treatment effects use 2-sided p values and 95% confidence intervals.

RESULTS

Baseline characteristics: The baseline characteristics of the 4 infarct categories and their treatment subgroups are listed in Table I. Approximately 64% of patients sustained a first AMI; the remaining 36% had at least 1 prior infarction, as defined previously on the basis of clinical or electrocardiographic grounds, or both. Among those with a first infarction, 27% had a non-Q-wave AMI, 44% an inferior Q-wave AMI, and 29% an anterior Q-wave AMI. Baseline characteristics were comparable between the 2 treatment groups in each electrocardiographic infarct category. Patients could be categorized into 2 hemodynamic subgroups as determined by ejection fraction and pulmonary congestion at study entry (Table I). Patients with first non-Q-wave or first inferior Q-wave AMI had higher mean ejection fractions (range 0.52 to 0.54) and a lower frequency of radiographic pulmonary congestion (range 10 to 16%) than patients with first anterior Q-wave or prior infarction (ejection fraction range 0.38 to 0.44; frequency of pulmonary congestion 24 to 26%).

End points: The first recurrent cardiac event rate and cardiac mortality rate for the entire follow-up period by electrocardiographic AMI subset, presence or absence of pulmonary congestion, and treatment assignment are summarized in Table II. Patients with first non-Q-wave or inferior Q-wave AMI had a lower first recurrent cardiac event rate and cardiac death rate with diltiazem than with placebo. Figure 1 shows the Kaplan-Meier life-table analysis for first recurrent cardiac event rate in the non-Q-wave myocardial infarction subset. By contrast, patients with a history and electrocar-

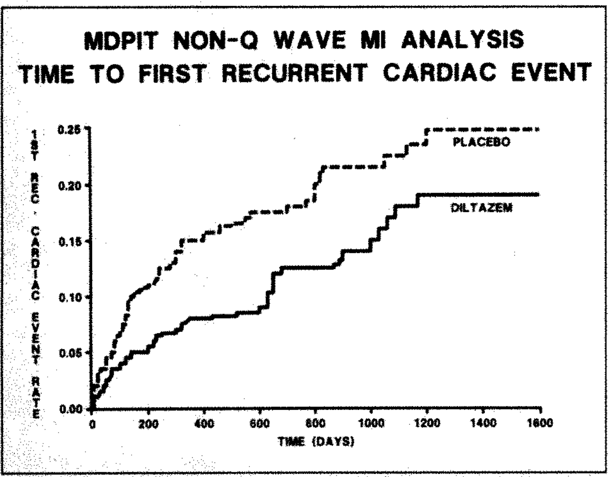

FIGURE 1. Kaplan-Meier life-table analysis of time to first recurrent (REC) cardiac event for the patients with acute non-Q-wave acute myocardial infarction (MI). MDPIT = Multicenter Diltiazem Post-Infarction Trial; *solid line*, diltiazem; *dashed line*, placebo.

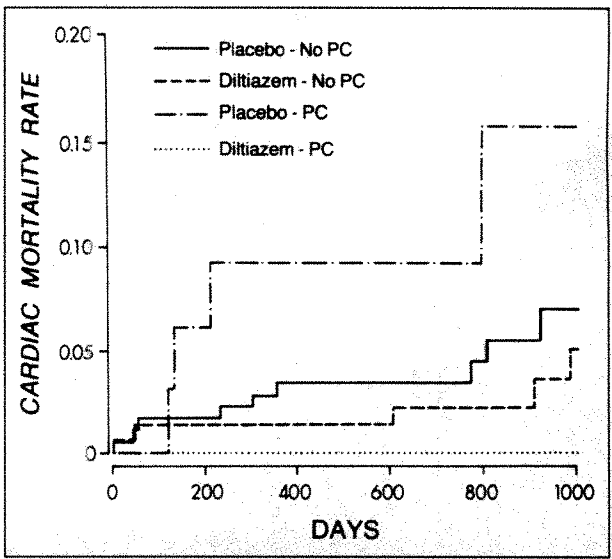

FIGURE 2. Cumulative rate of cardiac mortality for first non-Q-wave acute myocardial infarction according to the presence or absence of radiographic pulmonary congestion (PC), and diltiazem or placebo treatment assignment.

diographic evidence of prior infarction had a higher occurrence of these end points with diltiazem than with placebo. Thus, the bidirectional influence of diltiazem already shown with respect to pulmonary congestion[8,9] was also observed with respect to electrocardiographic infarct category.

These distinctions were sharpened by the additional examination of electrocardiographic subsets with and without pulmonary congestion. The Kaplan-Meier life-table analyses for first recurrent cardiac event rate and cardiac mortality rate are graphically illustrated in Figures 2 through 5. Decreased end point occurrence (cardiac mortality) was evident in diltiazem-treated patients having first non-Q-wave infarction with and without pulmonary congestion (Figure 2). Cardiac mortality was decreased in first inferior Q-wave infarction without pulmonary congestion but was not apparent in those having first inferior Q-wave infarction with pulmonary congestion (Figure 3). Conversely, increased end point occurrence was present in diltiazem-treated patients having first anterior Q-wave infarction (Figure 4) or prior myocardial infarction (Figure 5) with pulmonary congestion, but this adverse diltiazem treatment effect was absent in the same infarct categories without pulmonary congestion (Figures 4 and 5).

Electrocardiographic infarct category and presence or absence of pulmonary congestion had a combined influence that could be predicted from their relation to left ventricular function: Circumstances associated with more preserved function (first non-Q-wave or inferior infarction; no pulmonary congestion) led to the greatest reduction in cardiac events on diltiazem; and circumstances associated with more impaired left ventricular function (first anterior Q-wave or prior infarction; pulmonary congestion) led to the greatest increase in cardiac events with diltiazem.

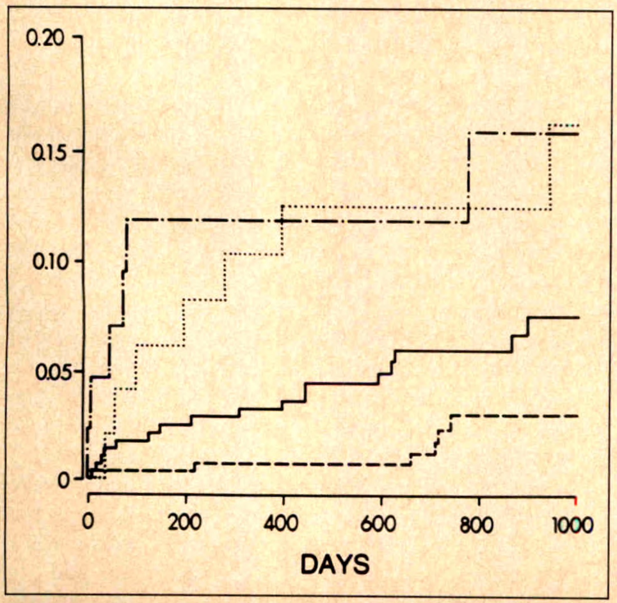

FIGURE 3. Cumulative rate of cardiac mortality for first inferior Q-wave acute myocardial infarction according to the presence or absence of radiographic pulmonary congestion, and diltiazem or placebo treatment assignment.

Multivariate analyses: Table III details the multivariate analyses using the Cox proportional-hazards regression model. Separate analyses were performed for the primary end point of a first recurrent cardiac event, as well as for cardiac death alone. Each analysis was conducted for the total study population of 2,377 patients, and for the population subdivided by the presence or absence of radiographic pulmonary congestion. A consistent relation emerged: The diltiazem:placebo hazard ratios for both trial end points were significantly less than unity (indicating a benefit from diltiazem) in patients having either first non-Q-wave or inferior Q-wave AMI. The diltiazem:placebo Cox hazard ratios for both

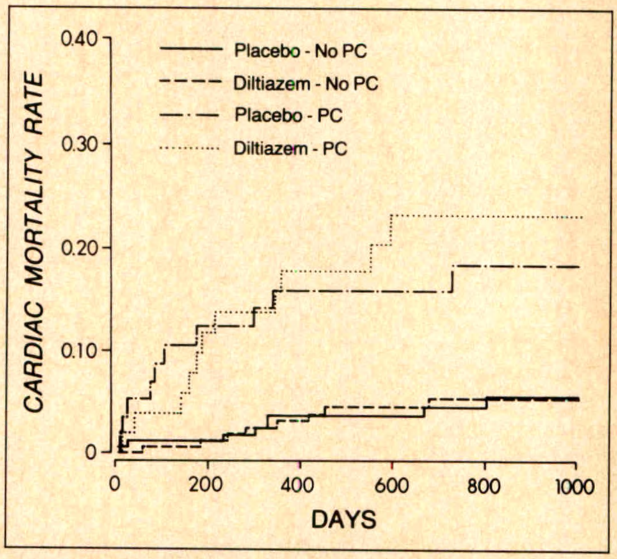

FIGURE 4. Cumulative rate of cardiac mortality for first anterior/anterolateral Q-wave acute myocardial infarction according to the presence or absence of radiographic pulmonary congestion (PC), and diltiazem or placebo treatment assignment.

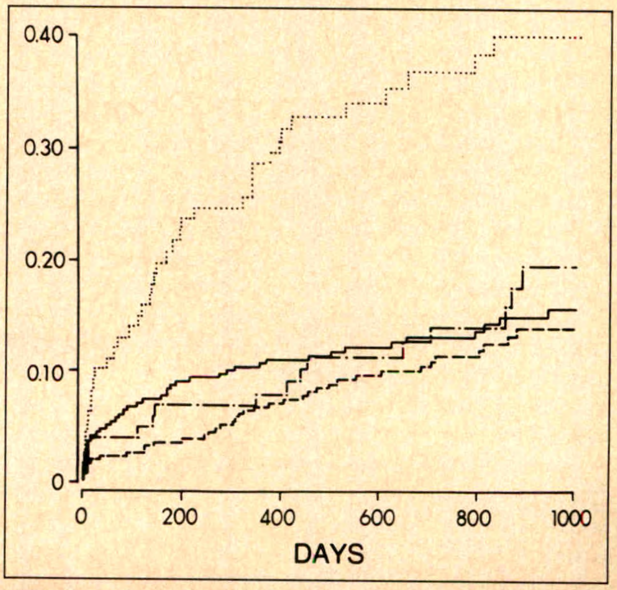

FIGURE 5. Kaplan-Meier life-table analysis for cardiac mortality in patients with at least 1 prior acute myocardial infarction and a superimposed new index infarct, according to the presence or absence of radiographic pulmonary congestion, and diltiazem or placebo treatment assignment.

TABLE III Effects of Treatment on Cardiac Death and First Recurrent Cardiac Events

	Total Population	No Pulmonary Congestion D:P Hazard Ratio* (95% Confidence Limits)	Pulmonary Congestion
Cardiac Death			
First non-Q AMI	0.46 (0.18, 1.21)	0.61 (0.22, 1.68)	†
First inferior Q AMI	0.53 (0.27, 1.06)	0.38 (0.15, 0.97)	1.27 (0.46, 3.50)
First anterior Q AMI	1.28 (0.68, 2.40)	1.11 (0.44, 2.83)	1.66 (0.67, 4.14)
Previous AMI	1.26 (0.90, 1.77)	0.75 (0.48, 1.18)	3.57 (1.95, 6.53)
First Recurrent Cardiac Event			
First non-Q AMI	0.48 (0.26, 0.89)	0.57 (0.30, 1.10)	†
First inferior Q AMI	0.66 (0.40, 1.09)	0.63 (0.35, 1.12)	1.01 (0.35, 2.92)
First anterior Q AMI	0.82 (0.51, 1.31)	0.62 (0.33, 1.16)	1.62 (0.73, 3.58)
Previous AMI	1.11 (0.85, 1.44)	0.85 (0.61, 1.20)	2.10 (1.30, 3.40)

* Ratio of the risk of end point events among patients receiving diltiazem to that among patients receiving placebo.

† Among patients with a first non-Q-AMI and pulmonary congestion, there were 4 cardiac deaths and 7 first recurrent cardiac events among the 35 patients given placebo, but no cardiac deaths and only 1 first recurrent cardiac event among 18 given diltiazem (see Table II). Because of the small numbers of patients involved in this latter subset and the paucity of end point events, reliable estimates of the hazard ratios for cardiac death and first recurrent cardiac event could not be obtained.

AMI = acute myocardial infarction; D:P = diltiazem: placebo.

end points were significantly greater than unity (indicating a detrimental effect from diltiazem) in patients with prior infarction complicated by pulmonary congestion. In fact, there was a gradation of ascending risk for both end points among electrocardiographic subsets of patients with radiographic pulmonary congestion who were treated with diltiazem (Table III). Cox hazard ratios in patients with previous infarction and pulmonary congestion were significantly higher than unity (with 95% confidence limits >1), indicative of a detrimental diltiazem effect in this subset. In some of the subset analyses, particularly those involving first non-Q-wave and inferior Q-wave AMI, the 95% confidence limits span unity; statistical power is reduced because of the small sample sizes in some of the analytic cells. Nevertheless, these data suggest a consistent strong pattern of diltiazem benefit in post-AMI patients with relatively intact left ventricular function.

Among patients with a first non-Q-wave AMI and pulmonary congestion, there were 4 cardiac deaths and 7 first recurrent cardiac events among 35 patients assigned to placebo, but no cardiac deaths and only 1 nonfatal reinfarction among the 18 patients assigned to diltiazem (Table II). Because of the small numbers of patients involved in this latter infarct subset, the imbalance between placebo (n = 35) and diltiazem (n = 18) treatment assignment, and the relative paucity of end point events, reliable estimates of the hazard ratios for cardiac death and first recurrent cardiac events could not be calculated with precision.

DISCUSSION

The findings from this comprehensive post hoc analysis indicate that the differential effect of diltiazem on outcome in several electrocardiographically categorized AMI subsets was influenced more by the underlying substrate of left ventricular function than by the electrocardiographic infarct subtype and location of damage. Our results do not permit any definitive conclusions regarding an exclusive diltiazem treatment effect in any particular subset of electrocardiographically defined AMI, although multivariate covariate analyses suggest a favorable long-term outcome with diltiazem in patients with a first non-Q-wave AMI and first inferior Q-wave AMI uncomplicated by pulmonary congestion. In contrast, there appeared to be an opposite, detrimental effect of diltiazem administration in patients with extensive infarction (first anterior Q-wave AMI; patients with at least 1 prior AMI and pulmonary congestion).

Prognostic importance of Q-wave versus non-Q-wave acute myocardial infarction in risk stratification: Several prior studies of risk stratification after AMI have firmly established the importance of left ventricular dysfunction as the major predictor of adverse outcome.[16–20] The results of a prospective risk stratification and survival study after AMI demonstrated measures of mechanical cardiac dysfunction either before or during the acute hospitalization (New York Heart Association functional class, pulmonary rales and ejection fraction) that were strongly and independently predictive of mortality during the first 2 years after infarction.[1] When angiographic variables obtained at cardiac catheterization were also included in statistical models assessing risk, left ventricular ejection fraction at rest, the number of diseased coronary arteries and occurrence of heart failure in the coronary care unit were the only independent predictors of survival using Cox regression analysis.[21,22]

Another approach to risk stratification has sought to correlate subsequent postinfarction prognosis based on the initial, or admission, electrocardiographic subtype (i.e., Q-wave versus non-Q-wave). A recent comprehensive review listed 35 reports, dating back to 1969, which detailed the prognosis and clinical course of non-Q-wave infarction.[23] This analysis, comprising pooled data on >15,000 patients with AMI, indicated a more favorable in-hospital mortality in non-Q-wave infarction (10%) than that in patients with Q-wave AMI (20%), despite a similar late mortality rate of 31 and 26%, respectively. Similarly, pooled data on 5,290 patients from 14 published studies dating back to 1976 showed an almost 3 times greater incidence of reinfarction after non-Q-wave (16%) than after Q-wave (6%) AMI.[23] Because of the strong clinical suspicion that coronary vasospasm was a principal factor in the genesis of reinfarction and reduced late survival after non-Q-wave AMI, the Diltiazem Reinfarction Study was undertaken to address the role of prophylactic diltiazem administration on in-hospital reinfarction. The results of this earlier study suggested a beneficial short-term reduction in nonfatal reinfarction in patients with non-Q-wave infarction.[10]

The present analysis indicated that diltiazem had a favorable long-term effect on recurrent cardiac events in patients with non-Q-wave infarction, as well as inferior Q-wave infarction. Thus, we did not find that the beneficial effect of diltiazem was uniquely confined to patients with non-Q-wave AMI. These 2 subsets, non-Q-wave and inferior Q-wave infarctions, had similar near-normal values for ejection fraction and low rates of radiographic pulmonary congestion, and the diltiazem: placebo hazard ratios were substantially less than unity in both groups, in contrast to the subsets of patients with prior infarctions and anterior AMI.

Our findings emphasize also that electrocardiographic AMI subtype, particularly if used as a singular criterion, may not be a uniformly reliable predictor of postinfarction prognosis. Freifeld et al[24] reported that any binary classification system of AMI as either "transmural" or "nontransmural," or as "Q-wave" versus "non-Q-wave," fails to distinguish major clinical and pathologic features, because strict morphologic (electrocardiographic) classification cannot accommodate the varied range of infarct patterns encountered anatomically within each electrocardiographic subgroup at necropsy. Accordingly, the designation of Q-wave or non-Q-wave infarction alone may tend to oversimplify outcome in various AMI subsets of patients whose magnitude of left ventricular dysfunction is minimal.

Importance of first versus prior acute myocardial infarction: We separated patients with prior infarction from those with first AMI by clinical history and by findings on the initial qualifying electrocardiogram. It is known that patients with prior infarctions are older, have more advanced coronary artery disease, and have more myocardial damage,[25] and such was the case in this study. We did not try to classify patients with prior infarction by electrocardiographic type and location because subsequent infarcts imply more extensive coronary artery disease, and such classification would have invariably resulted in many small analytic cells.

In patients with first infarctions, the electrocardiographic categorization of infarct type and location provided some indirect information about the extent of myocardial damage. Anterior Q-wave infarctions have been associated with more left ventricular dysfunction than that observed after non-Q-wave or inferior infarcts.[4-6] Q-waves in the anterior location have been associated with reduced ejection fraction and increased mortality.[7,26] Similar findings were observed in the patients given placebo in the current analysis.

Clinical implications: The results of this study suggest that long-term therapy with diltiazem may decrease the incidence of recurrent cardiac events in most patients after non-Q-wave or inferior Q-wave AMI. Such treatment, however, is not indicated for patients with multiple infarctions, or for patients who exhibit pulmonary congestion or other objective evidence of left ventricular dysfunction after a Q-wave infarction, regardless of electrocardiographic category. We wish to emphasize that these clinical guidelines are based on post hoc subset analyses from our extensive MDPIT database, and are not intended to represent definitive therapeutic recommendations.

Finally, MDPIT was performed before the widespread use of thrombolytic therapy for the treatment of AMI. Left ventricular function is well maintained in most patients treated with thrombolytic agents, especially those with first anterior Q-wave AMI.[27-29] The effect of diltiazem when administered to patients treated with thrombolytic therapy is not known. However, it is reasonable to assume that the bidirectional effects of diltiazem (favorable or unfavorable outcome) will be determined more by the status of left ventricular function in this patient group than by the presence or absence of Q-wave evolution. The results of these and other issues pertaining to the possible future role of diltiazem as adjunctive therapy after thrombolysis must await the outcome of the Thrombolysis In Myocardial Infarction-Phase III study, which is currently under way.

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Dynamic QRS-Complex and ST-Segment Monitoring in Acute Myocardial Infarction During Recombinant Tissue-Type Plasminogen Activator Therapy

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Changes of the QRS complex are the electrocardiographic expression of irreversible injury of the myocardium. In humans, the process of infarction occurs over several hours. A more rapid development of QRS changes has been reported in patients treated with thrombolytic agents. Patients with strongly suspected acute myocardial infarction (AMI) included in a placebo-controlled trial of 100 mg of recombinant tissue-type plasminogen activator (rt-PA) were monitored for 24 hours with continuous, on-line vectorcardiography. The magnitude of the QRS vector changes correlated with infarct size estimated by the maximal value of lactate dehydrogenase–1 (r = 0.69, p <0.001) as well as with left ventricular ejection fraction 30 days after randomization (r = 0.49, p <0.001). Treatment with intravenous rt-PA limited total QRS vector change but the QRS vector changes observed occurred more rapidly and reached a plateau 131 minutes earlier in patients treated with rt-PA than in those receiving placebo (p <0.01). A certain pattern of highly variable ST vector magnitude was identified and was associated with higher maximal lactate dehydrogenase–1 values (23 ± 13 vs 14 ± 10 μkat/liter, p <0.001) and a tendency to higher 1-year mortality (24 vs 9%, p = 0.08) than in patients without this pattern. In patients with this pattern, rt-PA did not affect maximal lactate dehydrogenase–1, time to maximal creatine kinase and final magnitude of QRS vector change.

(Am J Cardiol 1991;67:343–349)

Changes of the QRS complex are the electrocardiographic expression of irreversible injury of the myocardium.[1,2] Previous studies using repeated precordial mapping or standard 12-lead electrocardiography indicate that the process of necrosis as determined by electrocardiography may persist for up to 24 hours.[3–5] In patients treated with thrombolytic agents, enzymatic release has been shown to occur more rapidly, probably as a result of more rapid development of permanent myocardial damage (reperfusion injury).[6] A more rapid evolution of QRS changes has also been reported in studies using repeated recordings of standard 12-lead electrocardiography in patients receiving thrombolytic treatment.[7] No double-blind, randomized study has evaluated thrombolytic therapy using continuous QRS-complex and ST-segment monitoring. In the present study, we analyzed a subgroup of patients who were included in a randomized, double-blind trial of 100 mg of recombinant tissue-type plasminogen activator (rt-PA) or placebo given to patients strongly suspected of having an acute myocardial infarction (AMI). Electrocardiographic changes were not necessary for inclusion. The main results of that study have been published previously.[8]

Of 352 randomized patients, we monitored a subgroup of 103 patients with AMI with continuous on-line vectorcardiography during the initial 24 hours after inclusion in the trial. The rate and pattern of development and the magnitude of QRS-complex and ST-segment changes were studied in order to relate them to enzymatically estimated infarct size and left ventricular ejection fraction at 30 days (primary objectives) and to the severity and total duration of chest pain, as well as to in-hospital and 1-year mortality.

METHODS

Inclusion and exclusion criteria: Inclusion criteria in the Thrombolysis Early in Acute Heart Attack Trial was chest pain strongly suggestive of AMI lasting >15 minutes but <2 hours and 45 minutes in patients <75 years of age.

Exclusion criteria were increased risk of bleeding due to hemorrhagic diathesis, gastrointestinal or urogenital bleeding or treatment with anticoagulants, a recent history of stroke (within 6 months), uncontrolled hypertension (diastolic blood pressure >120 mm Hg), diabetic retinopathy, severe liver or kidney disease, ma-

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jor trauma (especially to the head) within the previous 6 months, childbearing capacity, suspected aortic dissection, previous participation in the study, alcoholism or any other reason for expecting poor compliance.

Patient series: Three hundred fifty-two patients were randomized to placebo (n = 177) or to rt-PA (n = 175). Because of a limited number of vectorcardiographic computers, the number of patients who could be monitored for 24 hours was limited to 178. Because these 178 represented a heterogeneous mixture of patients with AMI, unstable angina or noncardiac conditions, we report the findings from the 103 patients with a final diagnosis of AMI, established without the use of vectorcardiography.

Treatment and definitions: All patients received 5,000 units of heparin intravenously after randomization. A 10-mg bolus of rt-PA was administered intravenously, followed by an infusion of 40 mg over 48 minutes and of 50 mg over 2 hours and 30 minutes (100 mg in 3 hours 18 minutes) or the equivalent placebo. Immediately after completion of the blinded infusion, an intravenous infusion of heparin was begun and oral medication with coumarin initiated. The heparin infusion was continued for 3 to 5 days until a sufficient level of anticoagulation was achieved. All patients received 15 mg of metoprolol intravenously, followed by oral metoprolol 4 times a day unless contraindicated. Twelve to 24 hours after thrombolytic or placebo therapy was begun, patients received 125 mg of aspirin daily. Pain was evaluated hourly for the first 24 hours by the attending nurse, who asked the patient to indicate the severity of pain on a visual analog scale from 0 (no pain) to 10 (unbearable pain). The total duration of pain was calculated as well as the total pain score. Total serum creatine kinase was analyzed every 4 hours during the first 24 hours and the time from the initiation of therapy to the maximal value of creatine kinase was calculated for each patient. Creatine kinase MB-subunit was analyzed every 12 hours for the first 24 hours for diagnostic purposes. Lactate dehydrogenase–1 was analyzed every 12 hours for the first 72 hours. Myocardial infarct size was estimated using the maximal value of lactate dehydrogenase–1. A final diagnosis of AMI was made using prespecified criteria based on elevation of creatine kinase MB, electrocardiographic criteria and typical chest pain. Patients were followed up after 30 days, when an exercise test was performed and a radionuclide angiogram obtained. If residual ischemia was present, antico-

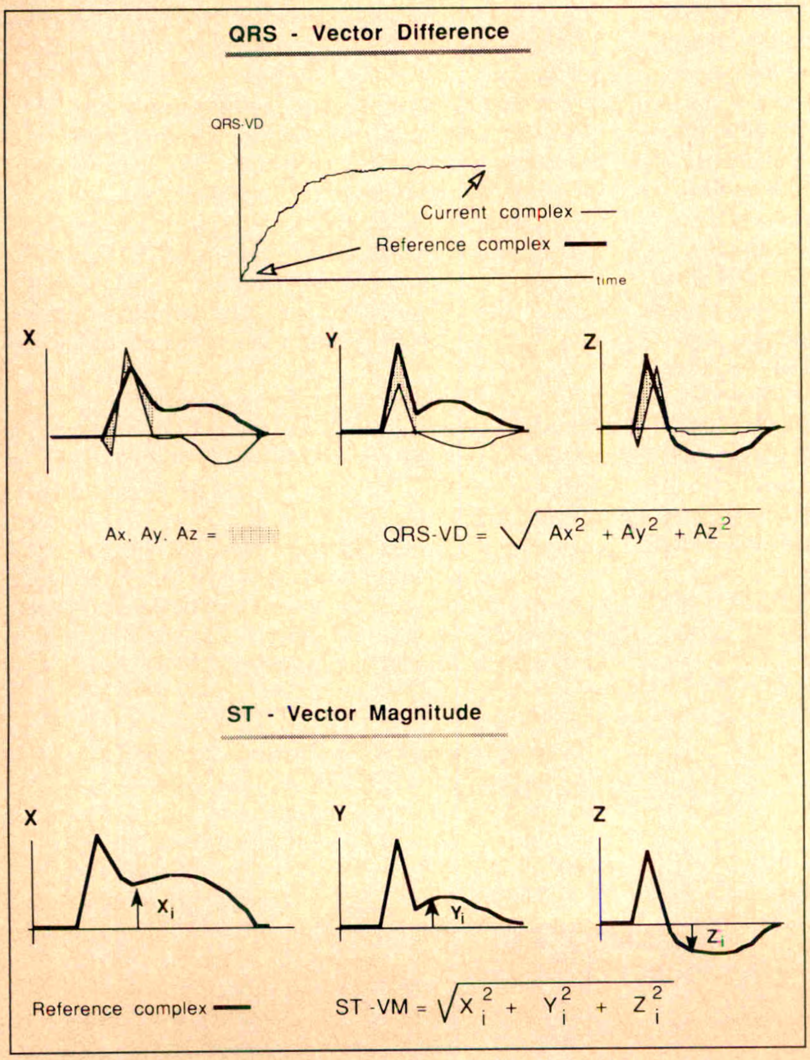

FIGURE 1. ***Top panel,*** **schematic drawing of a vectorcardiographic recording from a patient with an acute myocardial infarction. The reference mean QRS complex** ***(thick lines)*** **and the current mean QRS complex** ***(thin lines)*** **in leads X, Y and Z are plotted on top of each other.** ***Hatched area*** **is the QRS vector difference (QRS-VD) added according to the formula.** ***Bottom,*** **deviation** ***(arrows)*** **from baseline of the ST segment 20 ms after the termination of the reference QRS complex in each of the 3 leads (Xi, Yi and Zi). These, added according to the formula, constitute the ST vector magnitude (ST-VM). A = area of difference in lead x, y or z.**

agulation was continued and coronary angiography performed. When appropriate, coronary angiography was followed by coronary bypass surgery or angioplasty. None of our patients had coronary angiography within the first 24 hours. All patients were followed up after 1 year, when all surviving patients were clinically examined and all cardiovascular events, hospitalizations and interventions registered.

Continuous on-line vectorcardiography: The method has been described in detail previously.[9] We used a computerized system (MIDA 1000, Ortivus Medical, Täby, Sweden) for on-line, dynamic analysis of QRS-complex and ST-segment changes. Briefly, 8 electrodes are placed as described by Frank[10] and the 3 orthogonal leads X, Y and Z are continuously monitored and analyzed. After the operator accepts a template beat as the normal beat for that patient, the computer automatically discards all beats with a grossly different configuration. The accepted beats are then averaged every 2 minutes to form a "mean beat" for every 2-minute period, with the first 2-minute mean beat used as a reference for all further comparisons. All calculations are performed in real time and the result presented on a computer screen. Changes are related to the initial 2-minute reference mean beat for each patient and presented over time as trend curves. The 2 vectorcardiographic parameters studied were QRS vector difference and ST vector magnitude (Figure 1). The trendgraphs were evaluated by 2 independent observers. We previously reported a high degree of interobserver agreement.[8] Differences in identifying the points that follow were resolved by consensus. All trendgraph evaluations were completed and entered into a database before the study code was broken. On each individual trendgraph, the following 7 points were identified (Figures 2 [points 1 to 5] and 3 [points 6 to 7]): (1) the point where the QRS vector difference trendcurve reached a stable plateau; (2) the mean QRS vector difference level at 20 to 24 hours of recording; (3) the initial ST vector magnitude; (4) the maximal ST vector magnitude; (5) the time of decline of ST vector magnitude, i.e., the point on the curve at which the ST vector magnitude declined to a stable level.

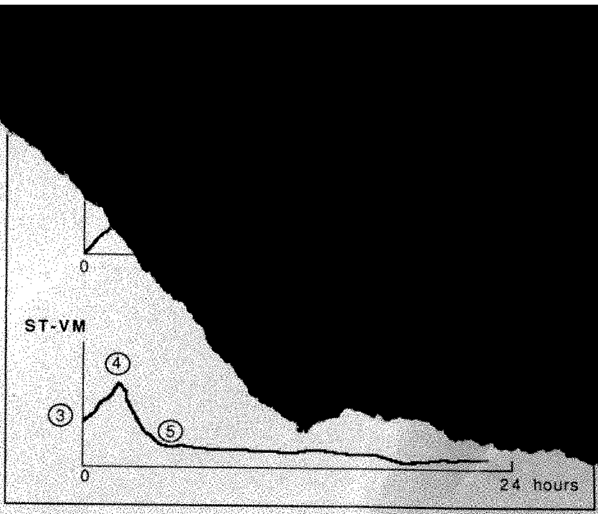

FIGURE 2. ***Top panel,*** **the point where the evolution of the QRS vector difference reaches a plateau in time and magnitude (1); the mean QRS vector difference between 20 and 24 hours of recording (2).** ***Bottom,*** **the magnitude of the initial ST vector magnitude (3); the maximal ST vector magnitude at any time during the first 4 hours of recording (4); the point in time when the ST vector magnitude trend curve declines to a stable plateau if it has been previously elevated for >30 minutes above 0.1 mV (5). Abbreviations as in Figure 1.**

(6) A pattern of rapid evolution of the QRS vector difference was retrospectively identified. The evolutionary pattern consisted of a QRS vector difference that increased rapidly and had a distinct breaking point, within 120 minutes of initiation of treatment and recording, after which a steady plateau was maintained for ≥30 minutes. A concomitant but otherwise unspecified decline of ST vector magnitude was also included in this pattern. This pattern was identified and patients were classified as having or not having this pattern after the study was completed but before the treatment code was broken.

(7) Before the treatment code was broken, patients were classified, according to the changes in ST vector magnitude level during the first 4 hours, into 4

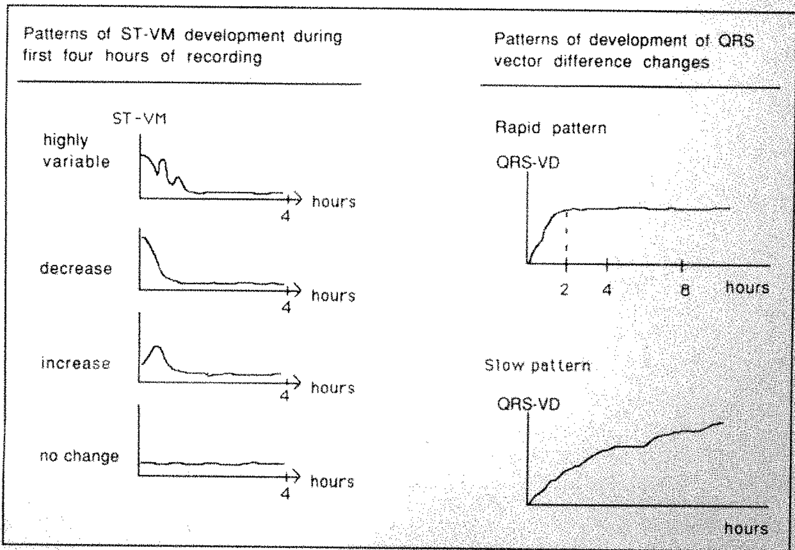

FIGURE 3. ***Left,*** **the 4 different types of ST vector magnitude trend curves.** ***Right,*** **rapid evolutionary pattern of QRS vector difference with the trend curve reaching a plateau within 2 hours from the start of recording. Abbreviations as in Figure 1.**

			Value
[illegible]	[illegible]	11	
[illegible]	[illegible]	17 (30)	
[illegible]	[illegible]	24 (43)	
[illegible]	[illegible]	13 (23)	
[illegible]	(4)	2 (4)	
[illegible]	1 (2)	5 (9)	
[illegible]	18 (38)	18 (32)	
Calcium antagonists	2 (4)	11 (20)	<0.05
Long-acting nitrates	3 (6)	11 (20)	0.09
Clinical status			
Hypotension (<90 mm Hg) (%)	3 (6)	4 (7)	
Rales present	13 (28)	15 (27)	
Systolic BP (mean mm Hg)	136	135	
Diastolic BP (mean mm Hg)	89	84	0.08
Heart rate (mean beats/min)	70	74	
Mean interval from onset of pain to start of infusion (min)	113	114	
Before hospital entry	8 (17)	14 (25)	
ST elevation at entry	42 (89)	44 (79)	0.23
Metoprolol i.v. at entry	29 (62)	33 (59)	
Mean time from onset of pain to start of VCG (min)	151	153	

Figures in parenthesis are percentages of all patients in each treatment group.
p >0.25 unless otherwise stated.
BP = blood pressure; i.v. = intravenous; rt-PA = recombinant tissue-type plasminogen activator; VCG = continuous vectorcardiography.

groups: "highly variable," "decrease," "increase" or "no change."

Statistical methods: Fisher's permutation test was used to compare the 2 treatment groups. Spearman's rank order correlation coefficient was used to measure the association between variables. All values are mean ± standard deviation, unless otherwise stated. A p value <0.05 was considered statistically significant.

RESULTS

In the present study, 103 patients with a final diagnosis of AMI, 56 treated with rt-PA and 47 with placebo, were monitored for 24 hours. Baseline characteristics were similar for the 2 treatment groups (Table I).

Correlations among vectorcardiographic parameters, enzymes and chest pain: The plateau of QRS vector difference reached after 24 hours correlated with maximal lactate dehydrogenase-1 (r = 0.69 [p <0.001]) and the initial ST vector magnitude correlated with maximal lactate dehydrogenase-1 (r = 0.63 [p <0.0001]). The maximal ST vector magnitude recorded correlated positively with the maximal value of lactate dehydrogenase-1 (r = 0.72 [p <0.001]). A weak correlation was observed between the total duration of pain and time to plateau of QRS vector difference (r = 0.174 [p = 0.02]) but there was no correlation between ST decline time and total duration of chest pain.

Correlation with left ventricular ejection fraction at 30-day follow-up: The correlation between the left ventricular ejection fraction at 30 days and the magnitude of the QRS vector difference after 24 hours was −0.49 (p <0.001).

QRS vector difference and ST vector magnitude: The QRS vector difference reached a plateau after 176 ± 155 minutes of recording in patients treated with rt-PA, compared to 307 ± 261 minutes (p <0.01) in the placebo group (Figure 4). The mean level after 24 hours was lower in the rt-PA than in the placebo group (25 ± 15 vs 35 ± 17 μVs [p <0.01]). The initial ST vector magnitude was 0.19 ± 0.13 mV in the rt-PA group and 0.25 ± 0.21 mV in the placebo group (difference not significant) and the ST vector magnitude declined to a stable level in 155 ± 115 minutes in patients treated with rt-PA versus 224 ± 143 minutes in the placebo group (p <0.05).

Duration of vectorcardiographic change: The mean time from the onset of chest pain until a plateau was reached in the evolution of the QRS vector difference was significantly shorter for patients treated with rt-PA (323 ± 153 vs 427 ± 235 min [p <0.001]). The cumulative percentage of patients who reached a plateau in the evolution of QRS vector difference is shown separately for the 2 treatment groups in Figure 5. At approximately 90 minutes after the start of the blinded treatment, the 2 curves begin to part so that, at any given time after that, the evolution of QRS vector dif-

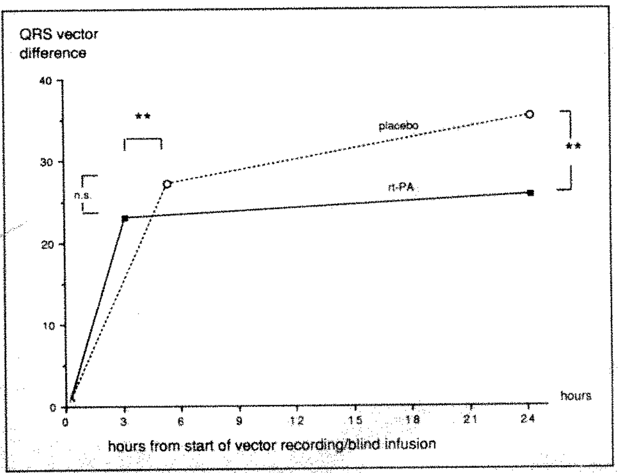

FIGURE 4. Rate of development and magnitude of QRS vector difference trend curves for the 2 treatment groups. ns = not significant; rt-PA = recombinant tissue-type plasminogen activator; ** = p <0.01.

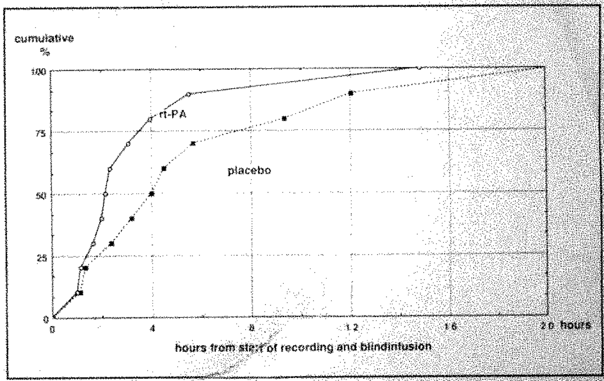

FIGURE 5. For each treatment group, the cumulative percentage of patients, who, at a given time from the start of blinded infusion, have reached a plateau in the evolution of QRS vector difference. Abbreviations as in Figures 1 and 4.

ference will have terminated in more patients treated with rt-PA than with placebo.

Patterns of QRS vector difference and ST vector magnitude change: A rapid pattern of evolution of the QRS vector difference was identified in 19 of 56 patients treated with rt-PA and in 2 of 47 in the placebo group ($p < 0.001$). Patients with a rapid pattern of evolution of the QRS vector difference had a significantly shorter ST decline time and also tendencies toward a shorter duration of chest pain and to lower in-hospital and 1-year mortality than patients without this pattern (Table II). The different patterns of ST vector magnitude variability seen during the first 4 hours showed a similar distribution among the 2 treatment groups. A highly variable pattern was observed in 34% of both groups; a decrease was observed in 13% (rt-PA) and 17% (placebo), an increase in 13 and 12%, respectively, and no change in 41 and 36%, respectively. Patients with a highly variable ST vector magnitude ($n = 34$) had a higher maximal lactate dehydrogenase-1 (23 ± 13 vs 14 ± 10 μkat/liter, $p < 0.001$), a higher magnitude of change in the QRS vector difference after 24 hours (37 ± 16 vs 26 ± 15 μVs, $p < 0.01$), a longer time to maximal creatine kinase (975 ± 370 vs 748 ± 409 min, $p < 0.01$), and a tendency toward a higher 1-year mortality (24 vs 9%, $p = 0.08$) than patients without this pattern ($n = 69$). Initial ST vector magnitude and maximal ST vector magnitude was significantly higher in patients with the highly variable ST vector pattern. In patients without the highly variable ST vector magnitude, treatment with rt-PA significantly reduced the maximal lactate dehydrogenase-1, the time to maximal creatine kinase and the QRS vector difference magnitude after 24 hours. Among patients with the highly variable ST vector magnitude, no effect of treatment with rt-PA on any of these parameters could be seen.

DISCUSSION

The overall results of the present trial indicated a reduction by 32% in maximum lactate dehydrogenase-1 and a significantly higher left ventricular ejection fraction at 30-day follow-up (59 vs 55%) among patients treated with rt-PA than with placebo.[8] Because of its protracted changes in plasma, the maximal value of lactate dehydrogenase-1 is suitable as a measurement of myocardial infarct size, even when thrombolytic therapy is administered.[6] Enzymatically estimated infarct size determined by the maximal value of lactate dehydrogenase-1 correlated moderately with the magnitude of the QRS vector difference after 24 hours ($r = 0.69$, $p < 0.001$). This finding agrees with those of Sederholm et al,[11] who found a positive correlation between QRS vector changes and enzymatic signs of myocardial damage. The high variability of the ST vector magnitude at an early stage of myocardial infarction may explain why, in the present study, the maximal ST vector magnitude showed a stronger correlation with the maximal value of lactate dehydrogenase than the initial ST vector magnitude. Sederholm et al[11] found a close correlation between maximal ST vector magnitude and enzymatically estimated infarct size using cumulative creatine kinase release.

TABLE II Changes of QRS Vector Difference in Relation to Treatment, Enzymatic Changes, ST Vector Magnitude Changes, and Clinical Outcome

	Rapid Pattern (n = 21)	Without Rapid Pattern (n = 82)	p Value
Maximal CK (μkat/liter)	34.9 ± 28.3	30.3 ± 23.0	
Maximal LDH-1 (μkat/liter)	20.4 ± 14.1	16.4 ± 11.6	
Initial ST vector magnitude (mV)	0.25 ± 0.17	0.21 ± 0.15	
Maximal ST vector magnitude (mV)	0.30 ± 0.20	0.27 ± 0.19	
Total pain duration (min)	655 ± 514	896 ± 516	0.06
ST decline time (min)	118 ± 63	209 ± 142	0.004
Treatment with rt-PA (%)	91	45	0.002
Hospital mortality (%)	4.7	11	
1-year mortality (%)	4.7	16	
Revascularization within 1 year (%)	33	17	0.14

$p > 0.25$ unless otherwise indicated.

CK = creatine kinase; LDH-1 = lactate dehydrogenase-1; rapid pattern = QRS vector differences reaching plateau within 120 minutes from start of recording; revascularization = coronary bypass surgery or percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue-type plasminogen activator; ST decline time = time from start of recording to ST vector magnitude has stabilized at normal level.

The relation between the total duration of chest pain and evolutionary time course of QRS vector difference was weak. This is in contrast with previous findings.[12] Intravenous β blockade is known to influence intensity and duration of chest pain[3] and, because 60% of the patients in the present study were treated with β blockade in a nonrandomized way, this may have influenced the time course of chest pain.

Left ventricular ejection fraction measured 30 days after inclusion in the trial showed a moderate correlation with the magnitude of the QRS vector difference after 24 hours ($r = -0.49$, $p < 0.001$). Palmeri et al[13] reported a correlation of 0.88 between left ventricular ejection fraction 3 weeks after AMI and a QRS score based on standard 12-lead electrocardiography. In their study, a relatively small variation in QRS score among patients with ejection fractions >55% was noted. In the present study, the mean ejection fraction at 30 days was 52%, and this may explain why the QRS vector difference correlated only moderately with ejection fraction.

With the vectorcardiographic technique described herein, we could demonstrate that the time from the onset of chest pain to the completion of the evolution of QRS vector difference was shortened by >2 hours by treatment with rt-PA, compared with placebo. Whether this rapid evolution of the QRS vector difference is due to relief of ischemia, which influences the QRS complex,[14] to reperfusion damage or to any other mechanism cannot be clarified in this study. Several other studies[7,15-17] support the finding that treatment with thrombolytic agents increases the rate of development of myocardial necrosis, documented electrocardiographically as well as enzymatically.

In the placebo group, the evolution of QRS vector difference was complete in 50% of patients within 4 hours from the start of blinded infusion (Figure 5), approximately 6 hours after the onset of chest pain. Large-scale studies of intravenous thrombolytic treatment found that thrombolytic therapy is most effective in restoring coronary flow and limiting infarct size when initiated within the first hours of the onset of symptoms.[18] However, it is also clear that the rate of infarct development, as determined by the evolution of QRS vector difference, varies within a wide time scale, supporting the findings that thrombolytic or other anti-ischemic therapy also has significant effects in some patients when initiated >6 hours after the onset of chest pain.[19,20]

The rate of decline of the ST vector magnitude significantly increased with rt-PA treatment, with the ST vector magnitude declining to a stable level 69 minutes earlier among patients treated with rt-PA than among the placebo group ($p < 0.05$). Previous studies using repeated multilead or precordial mapping electrocardiography indicated a more rapid decline of ST-segment changes when thrombolytic treatment is received, and this has also been shown to indicate reperfusion.[7,15-18,21,22] Trend analysis of the continuously monitored 12-lead electrocardiogram seems to improve sensitivity and specificity and makes it possible to detect reperfusion in individual patients also.[23] The present technique allows information from the QRS complex to be added to information from ST-segment changes. This may expand the time window for detection of electrocardiographic changes, because the evolution of QRS vector difference was completed 21 minutes (rt-PA) and 83 minutes (placebo) after the ST vector magnitude had declined to a normal level. The clinical value of QRS vector monitoring in this setting is not clear, although in a small pilot study we found that QRS vector monitoring may be useful for noninvasive detection of early coronary artery patency.[24]

We previously showed[9] that the majority of patients with an AMI who receive thrombolytic treatment exhibited a variable ST vector magnitude during the first 4 hours of recording. Other investigators using repeated short-interval electrocardiographic recording or precordial mapping also found ST-segment variation in the early hours of an AMI.[25] In the present study, 34% of the patients in both treatment groups showed a marked degree of variation of the ST vector magnitude during the first 4 hours. This may reflect variations in vessel tone or intermittent thrombus formation, although thrombus would be expected to form more frequently in the present placebo group. An alternative explanation is that the ST vector magnitude variation is due to intermittent occlusion by aggregates of thrombocytes. Most patients in the study received aspirin, but not until 12 to 24 hours had passed since treatment and vectorcardiographic recording had begun.

Based on coronary arteriographic findings, continuous 2-lead electrocardiographic monitoring and response to treatment with coronary vasodilators, Hackett et al[26] argued that ST-segment variability at an early stage of an AMI may be due to intermittent spasm. In a previous study, patients with the highly variable ST vector magnitude during the first 4 hours after initiation of thrombolytic therapy showed higher values of and longer time to maximal creatine kinase,[9] compared to patients without this variability. In the present study, this was confirmed, and a tendency toward an unfavorable prognosis was found. The effect of rt-PA on enzymatic and vectorcardiographic indexes of infarct size seemed to be limited to patients without the highly variable ST vector magnitude. This might support the concept that these patients have an increased vessel tone or recurrent platelet aggregates rather than a thrombus obstructing the flow.

Despite an initial similarity in the magnitude of ST vector changes, patients demonstrating a rapid evolutionary pattern of QRS vector difference tended to have a lower in-hospital and 1-year mortality, shorter pain duration and a higher need for revascularization within the first year after myocardial infarction than did patients with a slower pattern of development. The rapid pattern was significantly associated with a more rapid decline of ST vector magnitude to normal levels and with rt-PA treatment, which 91% of patients with the rapid pattern received (Table II). Treatment with rt-PA has been shown in other studies to result in a high degree of coronary patency, and reperfusion has been shown to accelerate the rate of electrocardiographic changes.[7,16,27,28]

Dynamic QRS-complex and ST-segment monitoring using continuous on-line vectorcardiography is a new method to monitor patients with AMIs. The magnitude of the QRS vector difference after 24 hours correlates with enzymatic infarct size, measured as the maximal value of lactate dehydrogenase–1 ($r = 0.69$), and correlates moderately with left ventricular ejection fraction measured at 30 days after randomization. The rate of evolution of the QRS vector difference varies within a wide range. Treatment with intravenous rt-PA results in a more rapidly evolving but finally lower magnitude of QRS vector difference. Distinct evolutionary patterns of QRS vector difference and ST vector magnitude may be observed and related to maximal lactate dehydrogenase–1, in-hospital and 1-year mortality, as well as to response to treatment with intravenous rt-PA.

Acknowledgment: We thank Kerstin Korssell and Ann-Marie Svensson for excellent technical assistance and Thomas Karlsson for statistical help as well as the nursing staff at the coronary care units at Östra Hospital and Sahlgrenska Hospital for their cooperation.

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Exercise Echocardiography and Technetium-99m MIBI Single-Photon Emission Computed Tomography in the Detection of Coronary Artery Disease

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To compare the relative diagnostic value of exercise echocardiography with perfusion technetium-99m metoxyisobutylisonitrile single-photon emission computed tomography (SPECT) in detecting coronary artery disease (CAD), 75 patients with suspected CAD but a normal electrocardiogram (ECG) at rest were included in a prospective correlative study. Both the exercise echocardiograms and SPECT studies were performed in conjunction with the same symptom-limited bicycle exercise test. The development of either a new wall motion abnormality or a reversible perfusion defect after exercise, or both, were regarded as a positive test for the exercise echocardiographic and SPECT studies, respectively. The results of these 2 diagnostic tests were compared with coronary arteriography.

Exercise echocardiography identified 35 (71%) and SPECT 41 (84%, $p = 0.13$) of the 49 patients with significant CAD (defined as >50% diameter stenosis). Twenty-five of the 26 patients (96%) without significant coronary stenosis had negative exercise echocardiographic results and 23 of 26 (88%) had negative SPECT results. Exercise-induced new wall motion abnormalities showed a good correlation with reversible perfusion defects, and the results of the 2 methods were concordant in 65 of 75 patients (agreement = 88%, $\kappa = 0.75 \pm 0.14$). Both the diagnostic accuracy of exercise echocardiography and SPECT were significantly higher than the exercise ECG (81 vs 64%, $p < 0.02$ and 88 vs 64%, $p < 0.005$). The sensitivity and specificity for detecting individual diseased vessels were 60 and 95% for exercise echocardiography and 67 and 94% for SPECT. However, in the 33 patients with 1-vessel disease, exercise echocardiography showed a lower sensitivity when compared with SPECT (61 vs 82%, $p < 0.02$). SPECT was tendentially more sensitive than exercise echocardiography in detecting isolated left circumflex coronary artery stenoses.

(Am J Cardiol 1991;67:350–355)

Myocardial perfusion scintigraphy and, more recently, exercise echocardiography have been widely applied in the noninvasive diagnosis of coronary artery disease (CAD). Important technologic developments have occurred in both techniques that have improved the quality of the images and thus enhanced their diagnostic value. Single-photon emission computed tomography (SPECT), by eliminating the superimposition of different myocardial regions inherent in planar scintigraphy, has improved the nuclear technique to diagnose and localize significant CAD.[1–3] The improvement of the echocardiographic equipment and the development of digital cine loop acquisition systems have overcome some of the practical and technical problems that had previously limited the application of exercise echocardiography.[4–6] Thus far, only limited data concerning the direct comparison of exercise echocardiography and planar 201-thallium scintigraphy are available.[7,8] However, the relative value of exercise echocardiography with a digital cine loop system versus SPECT imaging for the definition of CAD (for clinical decision making) has not been determined. We performed exercise echocardiography and SPECT during the same exercise test in a group of patients with clinically suspected CAD and a normal electrocardiogram (ECG) at rest. Their relative values in identifying and localizing significant coronary artery stenoses was the aim of this study.

METHODS

Study group: Between August 1989 and January 1990, 169 patients primarily referred for stress perfusion scintigraphy underwent simultaneous exercise echocardiography and SPECT imaging in our laboratory. Of the 93 patients in whom coronary angiography was performed within 2 months of the noninvasive studies, the 75 who had a normal ECG at rest (including flat T waves) were selected for the current study.

The mean age ± standard deviation of the 75 patients (65 men and 10 women) was 52 ± 12 years.

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Fourteen had a documented previous non-Q-wave myocardial infarction. At the time of the study, 27 patients were receiving antianginal therapy, including β blockers administered either alone (8 patients) or in combination with nitrates or calcium antagonists (9 patients). The remaining 9 patients were receiving calcium antagonists either alone (4 patients) or in combination with oral nitrates (5 patients). One patient was taking digitalis.

Exercise test procedure: All patients underwent a symptom-limited upright bicycle ergometry test with stepwise increments of 20 W each minute. Three electrocardiographic leads (lead II, V_2 and V_5) were continuously monitored. The level of the ST segment was calculated averaging the signal by a computerized system (Cardiovit CSG/12, Schiller). An ischemic response was defined as a ≥ 1 mm horizontal or downsloping ST depression persisting 80 ms after the J point.

SPECT imaging: Approximately 1 minute before the termination of the exercise, 370 mBq of technetium-99m metoxyisobutylisonitrile (MIBI) was injected into an antecubital vein. The exercise MIBI SPECT images were acquired 1 hour after exercise. Imaging was performed with a Siemens Gammasonics single-head Rota-Camera (Orbiter) equipped with 37 photomultiplier tubes, 3/8-inch NaI crystal and a low energy all-purpose collimator. Thirty-two projections with 6° increments (180° scanning) were obtained with acquisition time of 45 seconds per projection. The digitizing matrix (64 × 64 word mode) was selected in the midportion of the camera image by using a zoom factor $\sqrt{2}$. The tomographic data were processed on a Gamma 11 computer system with a floating point processor. Transaxial tomograms were reconstructed with the commercially available SPETS package (Nuclear Diagnostics AB, Hagsten, Sweden). The direction of the left ventricular long axis was determined from 2 orthogonal views (anterior and lateral). Oblique slices (short axis) and sagittal slices (vertical long axis), perpendicular and parallel to the long axis, respectively, were reconstructed. For each patient studied, 6 oblique (short axis) slices were defined from the apex to the base and 3 sagittal slices from the septum to the lateral wall.

For resting studies, patients were injected at rest with 370 mBq MIBI ≥ 24 hours apart from the exercise studies.

Exercise echocardiography: Two-dimensional echocardiograms were obtained at rest and immediately after the exercise test with the patients lying in the left lateral decubitus position. Multiple imaging sections, including conventional parasternal long and short axes, apical 2- and 4-chamber and apical long-axis planes were used. All images were obtained with a commercially available echocardiographic system (Hewlett Packard Sonos 1000). The rest and exercise images were both recorded on videotape and digitized on-line with a Nova Microsonics PreVue III System (ATL Co.). This system allows the recording at rest of 1 representative cardiac cycle obtained from 4 different views. After peak exercise, the digital system allowed the capture of 4 consecutive cardiac cycles for each view. The cycle with the best image quality could then be selected and displayed side by side with the correspondent rest images. Two different quad screen formats, showing the images before and after exercise, were finally stored in a 5 1/4-inch double-sided high-density floppy disk and subsequently reviewed as a continuous loop at various playback speeds.

Coronary angiography: All coronary angiograms were recorded using the Judkins technique. Significant CAD was visually defined as $\geq 50\%$ narrowing of the luminal diameter of ≥ 1 coronary arteries or of 1 of their major branches.

Interpretation of exercise echocardiography and SPECT: The analysis of the echocardiographic images was performed by 1 experienced observer unaware of scintigraphic and angiographic data. Left ventricular wall motion was visually evaluated and graded as normal = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4. A postexercise wall motion score index was calculated by summing the scores assigned to each segment and dividing by the number of segments. By comparing in a side-by-side manner the rest and postexercise images, an ischemic response was defined as the development of a new wall motion abnormality in the study after exercise.

To compare rest and exercise SPECT images, the short- and the vertical long-axis slices were used. Each of the 6 short-axis slices were divided into 8 equal segments, yielding a total of 48 segments. The apical region was assessed from the 3 central sagittal cross sections, yielding a total of 51 segments. All the SPECT studies were interpreted by 2 experienced observers, unaware of echocardiographic and angiographic results, using a 5-point visual scoring system (1 = normal, 2 = doubtfully decreased uptake, 3 = mildly decreased uptake, 4 = severely decreased uptake, and 5 = "absence" of uptake). A semiquantitative score index was calculated by summing the score of each segment and dividing by the number of all the segments. An ischemic response was diagnosed when the stress images showed a significant perfusion defect (score ≥ 3 in ≥ 2 contiguous segments), which partially or completely normalized in the rest images.

In our laboratory inter- and intraobserver agreement for exercise echocardiography was 91% ($\kappa = 0.81$, standard error of the mean [SEM] = 0.14) and 92% ($\kappa = 0.84$, SEM = 0.2) for exercise echocardiography and 85% ($\kappa = 0.70$, SEM = 0.23) and 90% ($\kappa = 0.8$, SEM = 0.22) for SPECT.

Assignment of different left ventricular region to specific coronary arteries: To assign the vascular territories of the different coronary arteries, the 51 left ventricular segments, imaged by SPECT, were combined in 5 major regions (Figure 1). Similarly, the 14 echocardiographic segments were grouped in the same corresponding ventricular regions, denoted as: anterior (segments 2 and 7), posterolateral (segments 3 and 8), inferior (segments 4 and 9), interventricular septum, which was subdivided into anterior (segments 1 and 6) and posterior (segments 5 and 10), and apex (segments 11, 12, 13 and 14) (Figure 2).

For both techniques, the vascular territory of the left anterior descending artery included the anterior wall and anterior septum; the inferior wall was considered to

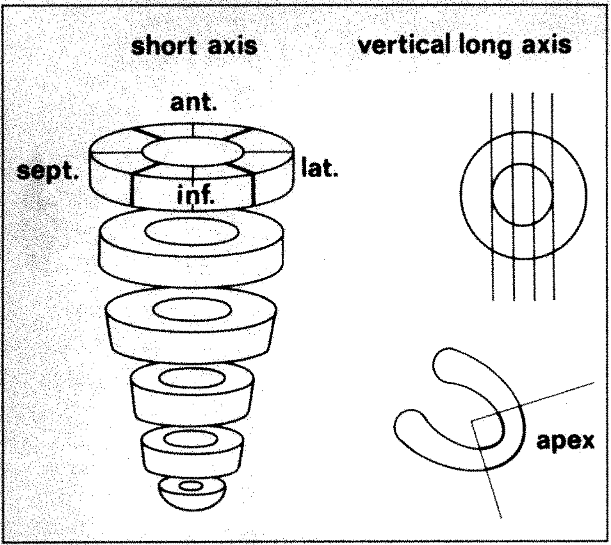


FIGURE 1. Representation of single-photon emission computed tomography imaging. The 6 short-axis and the 3 vertical long-axis slices were used for analysis of the studies. The left ventricle was divided into 5 major regions: interventricular septum (sept.), anterior (ant.) wall, lateral (lat.) wall, inferior (inf.) wall and apex.

represent the vascular bed of the right coronary artery and the posterolateral wall of the left circumflex artery. The attribution of the posterior septum and of the apex was more flexible, depending on the coexistent abnormalities in the adjacent regions. In case of an isolated apical defect, the defect was attributed to the vascular territory of the left anterior descending artery.

Statistical analysis: McNemar's test was used to assess the significance of the differences between sensitivities, specificities and accuracies. P values <0.05 were considered significant. The agreement between techniques was defined as the percentage of concordant diagnosis and it was also assessed by calculating the κ value and its SEM. Wall motion and perfusion score indexes were compared using standard correlation statistics.

TABLE I Overall Diagnostic Values for Coronary Artery Disease of Digital Exercise Echocardiography, SPECT and Electrocardiogram

	Sensitivity	Specificity	Accuracy
ECHO	71% (35/49)	96% (25/26)	81% (61/75)
SPECT	* 84% (41/49)	88% (23/26)	88% (65/75) †
	‡		‡
ECG	55% (27/49)	81% (21/26)	64% (48/75)

* =p <0.05; † = p <0.02; ‡ = p <0.005.

ECG = electrocardiogram; SPECT = single-photon emission computed tomography.

RESULTS

No adverse clinical consequences resulted from the exercise testing. Thirty-four patients (45%) attained at least the 85% of their age-predicted maximal heart rate. Angina pectoris occurred in 16 (21%) and ischemic ST-segment depression in 32 patients (43%). The intervals between the end of the exercise and the recording of the first and the last echocardiographic images were 22 ± 13 seconds (range 6 to 50) and 80 ± 33 seconds (range 35 to 150), respectively. The rest echocardiograms showed normal left ventricular wall motion in 71 patients; 4 patients had mild localized wall motion abnormalities (hypokinesia of 1 or 2 segments), whereas definite perfusion defects in the rest scan were found in 5 patients. In all these patients a worsening of wall motion and perfusion was seen after exercise. Resting wall motion and perfusion abnormalities were concordant with

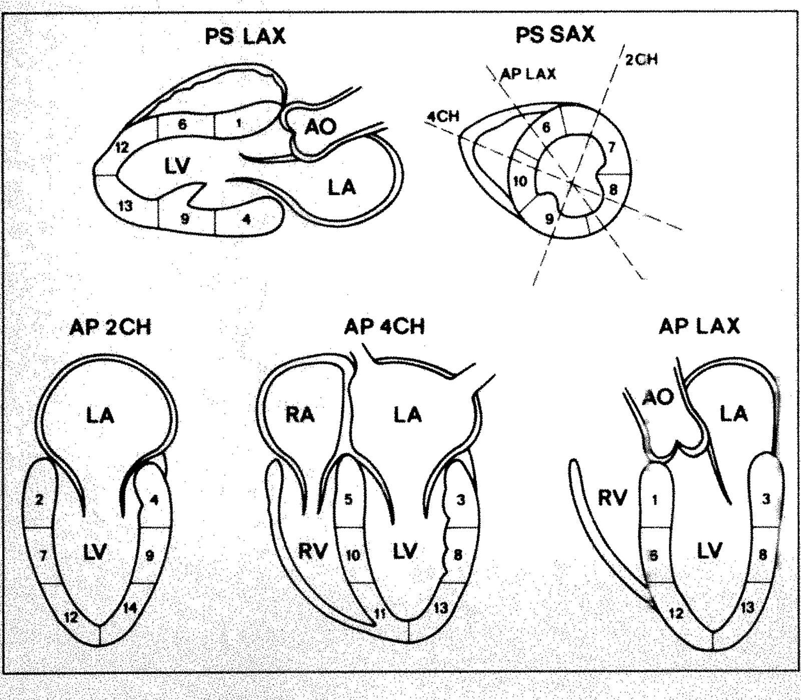


FIGURE 2. The 14 left ventricular segments analyzed by echocardiography. Anterior region comprised segments 2 and 7; posterolateral, segments 3 and 8; inferior region, segments 4 and 9; posterior septum, segments 5 and 10; anterior septum, segments 1 and 6; apex, segments 11, 12, 13 and 14. AO = aorta; AP4CH = apical 4-chamber view; AP2CH = apical 2-chamber view; APLAX = apical long-axis view; LA = left atrium; LV = left ventricle; PSLAX = parasternal long-axis view; PSSAX = parasternal short-axis view; RA = right atrium; RV = right ventricle.

TABLE II Ergometric, Scintigraphic and Angiographic Data in Patients with False-Negative Exercise Echocardiography

Pt. No.	MW (W)	%MHR (beats/min)	AP	ST	BB	SPECT	LAD	LC	Right	Time from Exer. to Echo*
1	160	59	+	0	0	0	+	+	0	20–60
2	140	99	0	0	0	0	0	0	+	13–58
3	160	90	0	+	0	+(PL)	0	+	0	24–114
4	150	80	0	0	0	+(PL)	0	0	+	32–110
5	160	90	0	0	0	0	0	+	0	16–83
6	120	100	0	0	0	0	0	+	0	12–50
7	180	70	0	+	0	0	0	+	0	10–50
8	140	80	+	0	0	0	+(diag)	0	0	30–110
9	140	81	0	+	+	+(S,A)	+	0	0	20–120
10	160	91	0	+	0	+(I)	0	+	0	15–60
11	140	82	0	+	0	0	+	0	0	30–120
12	140	90	0	0	+	+(PL)	0	+	0	30–85
13	100	64	0	0	+	+(PL)	0	+	0	20–115
14	148	60	0	+	+	+(PL,A)	0	+	0	15–115

* The numbers represent the time interval (seconds) between the peak exercise and the acquirement of the first and of the last echocardiographic view, respectively.

A = anterior; AP = angina pectoris; BB = β blockers; Diag = diagonal branch; exer. = exercise; I = inferior; LAD = left anterior descending artery; LC = left circumflex artery; MHR = maximal heart rate; MW = maximal work load; OM = obtuse marginal branch; PL = posterolateral; Right = right coronary artery; S = septal; SPECT = single-photon emission computed tomography; ST = ST segment.

+/0 = presence/absence of angina, ST-segment depression, β-blocker therapy, transient perfusion defect, coronary diameter stenosis >50%.

the site of infarction in 3 and 4 patients, respectively. Forty-nine patients (65%) had >50% diameter stenosis of ≥ 1 of the coronary arteries; of these, 16 had a multiple vessel disease. Twenty-six had either normal or not significantly diseased vessels.

Sensitivity and specificity for the identification of coronary artery disease: The overall sensitivity, specificity and accuracy of exercise echocardiography, SPECT and electrocardiography in detecting CAD are listed in Table I. Exercise echocardiography and SPECT showed sensitivities of 71 and 84% ($p = 0.13$), which were significantly higher than that obtained by ECG ergometry (55%, $p < 0.05$ and $p < 0.005$, respectively). Among the 26 patients without significant CAD, 25 had normal exercise echocardiography and 23 normal SPECT. The overall accuracies of 81% for echocardiography and of 88% for SPECT were significantly greater than by exercise ECG.

The effect of the number of abnormal vessels present on the ability to obtain an ischemic response by the different techniques is shown in Figure 3: In patients with 1-vessel disease, SPECT showed a greater sensitivity than exercise echocardiography ($p < 0.05$). In patients with multiple vessel disease, 15 and 14 of 16 were identified, respectively, as ischemic by exercise echocardiography and SPECT. Table II summarizes the ergometric, scintigraphic and angiographic data in the 14 patients with false-negative echocardiographic results. Nine of these had negative ECGs and 7 also had false-negative SPECT. A 1-vessel disease was found in 13 patients and only 1 patient had multivessel disease.

Agreement between echocardiography and SPECT for the diagnosis of ischemia: Figure 4 shows the relation between the final diagnosis provided by exercise echocardiography and SPECT. Sixty-five of 75 patients were concordantly classified (agreement = 88%, $\kappa \pm$ SEM = 0.75 ± 0.14). In the 35 patients with ischemic response detected by the 2 methods, wall-by-wall com-

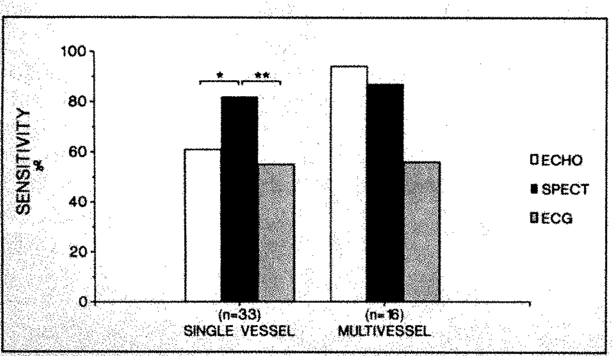
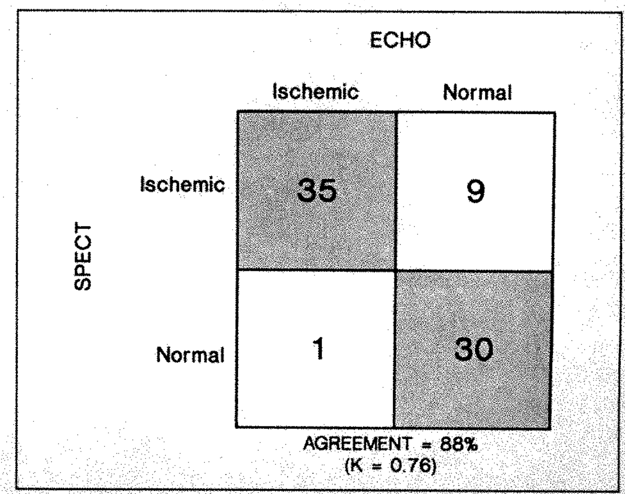


FIGURE 3. Comparison of the sensitivities of exercise echocardiography (ECHO), single-photon emission computed tomography (SPECT) and electrocardiography (ECG) in patients with 1- and multivessel disease. * = $p < 0.05$; ** = $p = 0.02$.



SPECT	ECHO Ischemic	ECHO Normal
Ischemic	35	9
Normal	1	30

AGREEMENT = 88%
(K = 0.76)

FIGURE 4. Agreement between exercise echocardiography (ECHO) and single-photon emission computed tomography (SPECT) in diagnosing ischemia.

TABLE III Detection of Individual Coronary Artery Stenoses with Exercise Echocardiography and SPECT

	Echocardiography			SPECT		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Total	60 (42/70)	95 (146/155)	84 (188/225)	64 (47/70)	94 (145/155)	85 (192/225)
LAD	69 (20/29)	98 (45/46)	87 (65/75)	66 (19/29)	96 (44/46)	84 (63/75)
LC	45 (11/24)	96 (49/51)	80 (60/75)	67 (16/24)	96 (49/51)	87 (65/75)
Right	65 (11/17)	89 (52/58)	84 (63/75)	70 (12/17)	89 (52/58)	85 (64/75)

Values are expressed as percentage and as absolute numbers.
Abbreviations as in Table II.

parison of transient wall motion and perfusion defects demonstrated a complete correspondence in 28, a partial correspondence in 5 and no correlation in 2. When the exercise wall motion and perfusion scores indexes were compared, they were positively correlated ($r = 0.75$; $p < 0.001$).

Localization of individual coronary artery stenoses: The detection of individual narrowed arteries by each technique is presented in Table III. Exercise echocardiography correctly identified 42 of the 70 stenosed arteries (60%) and 146 of the 155 normal vessels (95%). SPECT correctly identified 47 of the 70 stenosed arteries (67%) and 145 of the 155 normal vessels (94%).

Figure 5 shows the comparison of the sensitivities for individual lesions in patients with 1-vessel disease. In this subset, only 5 of 13 left circumflex lesions were detected by exercise echocardiography, whereas SPECT correctly identified 10 of them ($p = 0.07$). In contrast, both techniques showed a similar ability to predict left anterior descending and right coronary artery stenoses.

DISCUSSION

This is the first study in which exercise echocardiography and technetium-99m SPECT imaging have been simultaneously tested to detect the presence of CAD in a large group of patients with a normal ECG at rest. The main findings of this study are (1) that stress echocardiography and SPECT have a good agreement and have a similar diagnostic accuracy, which is superior to that of exercise electrocardiography (Table I), and (2) that SPECT is only slightly superior to exercise echocardiography in detecting 1-vessel disease in patients with a stenosis of the left circumflex coronary artery (Figure 5).

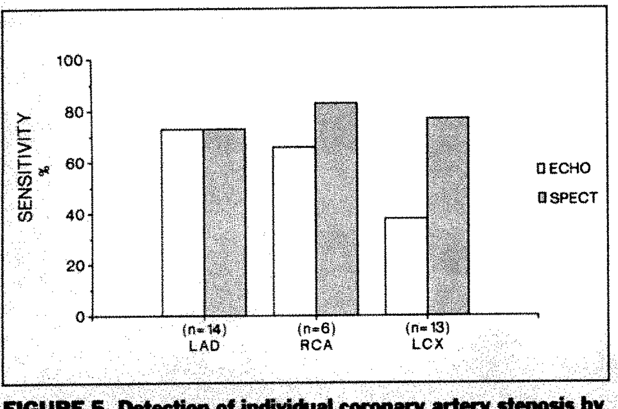


FIGURE 5. Detection of individual coronary artery stenosis by exercise echocardiography (ECHO) and single-photon emission computed tomography (SPECT) in patients with 1-vessel disease. LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

In a study by Maurer and Nanda,[7] exercise echocardiography and planar thallium-201 scintigraphy were performed in a group of patients referred for coronary arteriography. The tests provided a sensitivity of 83 and 78%, respectively. They found a sensitivity for exercise echocardiography that was better than in our study (83 vs 71%), whereas our SPECT results had a similar sensitivity when compared with planar scintigraphy used in their study (84 vs 78%). However, the results of these studies are difficult to compare directly because of different patient selection: our patients were primarily referred for stress scintigraphy, whereas patients in the other study were primarily referred for coronary arteriography, and more severe CAD may have been present. This can account for the slightly better results of exercise echocardiography relative to perfusion imaging in the study by Maurer and Nanda. Similar results have been reported by other investigators.[4,5,9] Recently, Ryan et al,[6] in patients with chest pain and normal left ventricular wall motion at rest, found a sensitivity of 78% and a specificity of 100% compared with lesions of >50% on coronary arteriography. In addition, these investigators found the lowest sensitivity in patients with 1-vessel disease of the left circumflex coronary artery, which is consistent with our findings. Furthermore, the use of antiischemic drugs may reduce the sensitivity of both perfusion scintigraphy and stress echocardiography.[10,11]

We found that SPECT has higher sensitivity than echocardiography in detecting patients with 1-vessel disease. Transient perfusion defects may occur early and do not always lead to a wall motion abnormality. The latter results when more pronounced ischemia is present. Thus, exercise echocardiography may be negative when a perfusion defect is detected, which may explain its lower sensitivity. In some patients, wall motion abnormalities recover very rapidly after the cessation of exercise, which may further explain a lower sensitivity of stress echocardiography, because its acquisition is done in the immediate postexercise phase and not at peak exercise.[12]

In contrast to patients with 1-vessel disease, echocardiography and SPECT had a similar diagnostic efficacy in patients with multiple vessel disease. Moreover, in this study few patients with multiple vessel disease were included and therefore the results cannot be considered conclusive.

Study limitations: Our patients were referred for scintigraphy for a variety of reasons, such as a nondiagnostic electrocardiographic exercise test, the localization and quantification of ischemia, and the assessment of the functional significance of the coronary stenosis before intervention. Thus, the results cannot be directly compared with patients selected on the basis of other criteria. Second, both exercise echocardiography and SPECT studies were visually analyzed. Although the quantitative analysis of exercise echocardiograms is hampered by technical difficulties, its application to SPECT has enhanced its diagnostic power.[2]

In conclusion, exercise echocardiography and SPECT, directly compared in a series of patients with a normal ECG at rest, provide similar overall information for the noninvasive diagnosis of CAD. A strong correlation between the 2 techniques for identifying localizing and quantifying ischemia was found. SPECT imaging, however, appears to be superior to exercise echocardiography in patients with 1-vessel disease, particularly of the left circumflex coronary artery.

Acknowledgment: We gratefully acknowledge Jan Thijssen, PhD, for statistical advice. We also thank all the technicians of the Nuclear Medicine Department for their cooperation in performing the combined echocardiographic and nuclear studies.

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Impaired Left Ventricular Filling and Regional Diastolic Asynchrony at Rest in Coronary Artery Disease and Relation to Exercise-Induced Myocardial Ischemia

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Impaired left ventricular (LV) diastolic filling at rest is frequently observed in patients with coronary artery disease (CAD) who have normal LV systolic function and no previous infarction. To test the hypothesis that abnormal diastolic function at rest might reflect the functional severity of CAD, as estimated by exercise-induced ischemia, the relation between regional and global LV diastolic function at rest and during exercise-induced ischemia was evaluated in 49 patients with radionuclide angiography. All patients had normal systolic function at rest. Group 1 (n = 26) patients manifested a normal ejection fraction response to exercise and group 2 (n = 23) patients an abnormal response. Data obtained from 22 age-comparable normal volunteers were used for comparison. Although regional and global diastolic function were not different between normal subjects and group 1 patients, peak filling rate was lower in group 2 patients than in normal subjects (2.5 ± 0.8 vs 3.2 ± 0.6 end-diastolic counts/s; $p < 0.01$). Moreover, regional diastolic asynchrony, as assessed from the radionuclide data by using a regional sector analysis of the LV region of interest, was greater in group 2 patients (46 ± 44 ms) than in both normal subjects (25 ± 16 ms; $p < 0.05$) and group 1 patients (23 ± 16 ms; $p < 0.05$). Thus, among patients with CAD and with normal LV systolic function at rest, impaired LV filling and regional asynchrony predict a greater degree of exercise-induced ischemia, suggesting a greater extent of jeopardized myocardium.

(Am J Cardiol 1991;67:356–360)

Impaired left ventricular (LV) diastolic function is evident at rest in many patients with coronary artery disease (CAD) who have normal global and regional systolic function at rest. Such patients also manifest regional diastolic asynchrony,[1,2] and the degree of asynchrony correlates with global impairment of LV diastolic filling.[3-5] The relation between the abnormalities of regional and global diastolic function at rest and during exercise-induced ischemia has not been established. In the current study, we hypothesized that diastolic asynchrony and impaired global diastolic filling in patients with CAD might reflect the functional severity of CAD and thus might be related to the magnitude of reversible ischemia, as assessed by the ejection fraction response to exercise. Accordingly, we evaluated LV diastolic filling characteristics and diastolic asynchrony at rest in relation to the occurrence of exercise-induced ischemia in patients with CAD without previous myocardial infarction.

METHODS

Patient groups: We studied 49 patients (40 men, 9 women, mean age ± standard deviation 52 ± 9 years, range 35 to 71) with CAD by radionuclide angiography. All patients underwent coronary arteriography. Measurement of LV end-diastolic pressure was obtained in 19 patients. Patients were enrolled in the study if they: (1) had significant CAD, defined as ≥50% reduction in luminal diameter of at least 1 major coronary artery by coronary angiography; (2) had normal LV radionuclide ejection fraction at rest (≥45%)[6]; (3) had normal LV regional wall motion at rest by both radionuclide angiography and contrast ventriculography; (4) had neither a history nor electrocardiographic evidence of previous myocardial infarction; and (5) had no evidence of conduction abnormalities on the electrocardiograms. Finally, studies were performed in all patients after discontinuation of calcium antagonists and β blockers for ≥48 hours, long-acting β blockers for ≥72 hours, and nitrate preparations for ≥6 hours.

Patients were divided into 2 groups according to the ejection fraction response and regional wall motion during exercise. Group 1 (n = 26) comprised patients with a normal ejection fraction increase (≥5% compared with the basal value) during exercise with no regional wall motion abnormalities. Group 2 (n = 23) comprised

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patients with an abnormal ejection fraction response during exercise, ranging from −21 to 4% (mean −7 ± 7%), with or without new regional wall motion abnormalities. Patients in group 2 were slightly, but significantly, older than those in group 1 (Table I).

The radionuclide data obtained in patients with CAD were compared with those from 22 asymptomatic, age-comparable normal volunteers without any evidence of cardiovascular disease on the basis of history, physical examination, electrocardiogram and echocardiogram. The normal group comprised 13 men and 9 women ranging in age from 40 to 74 years.

All normal control subjects and 31 patients with CAD underwent 2-dimensional echocardiography to measure LV end-diastolic dimension and wall thickness, including 13 group 1 and 18 group 2 patients. In the remaining 18 patients with CAD, echocardiograms were not of interpretable quality. No patient had echocardiographic evidence of LV hypertrophy (wall thickness ≥13 mm).

Gated blood pool scintigraphy: Radionuclide angiography was performed at rest and during exercise. Red blood cells were labeled in vivo with 15 to 25 mCi of technetium-99 and imaging was performed with a conventional Anger camera equipped with a highly sensitive, parallel hole collimator oriented in a modified left anterior oblique position. A total of 7.5 to 10.5 million counts were collected for each rest study. All subjects then underwent maximal supine bicycle exercise, beginning at a work load of 25 W, with a 25-W increase every 2 minutes. Heart rate and rhythm were recorded continuously and blood pressure was measured at each stage during exercise. Exercise radionuclide angiographic data corresponded to the final 2 to 2.5 minutes of exercise.

High-temporal resolution (20 ms/frame) cardiac image sequences were constructed by computer-based electrocardiographic gating, using list mode data acquisition, with exclusion of extrasystolic and postextrasystolic beats and combined forward and reverse gating from the R wave.[7] LV time-activity curves, representing relative changes in LV volume during the average cardiac cycle, were generated from the cardiac image sequence after background correction with a fixed region of interest, which was drawn manually to conform to the borders of the left ventricle.

Analysis of global left ventricular function: Indexes of global LV function were derived by computer analysis of the background-corrected time-activity curve. Ejection fraction was computed on the basis of relative end-diastolic and end-systolic counts. Peak filling rate was computed by fitting a third-order polynomial function to the rapid diastolic filling portion of the time-activity curve by a least-squares technique, normalized for the number of counts at end diastole and expressed as fractional end-diastolic counts per second (EDC/s).[6] Time to peak filling rate was measured relative to end systole (minimal volume on the time-activity curve).

Analysis of regional left ventricular nonuniformity: The LV region of interest was divided into 20 sectors of equal arcs (18°), each emanating from the end-diastolic LV center of gravity, as previously described.[8] The inner one-third of each sector was excluded, yielding anular sectors comprising the outer two-thirds of the left ventricle. From these fixed regions, sectorial time-activity curves were constructed.

TABLE I Characteristics of the Study Groups

	Normal Subjects	CAD Group 1	CAD Group 2
Age (yr)	51 ± 9	49 ± 8	56 ± 8*
Sex (m/f)	13/9	22/4	18/5
Heart rate (beats/min)			
Rest	67 ± 13	66 ± 10	69 ± 10
Exercise	135 ± 15	124 ± 22	107 ± 13†
Systolic blood pressure (mm Hg)			
Rest	124 ± 16	126 ± 15	137 ± 15§
Exercise	171 ± 26*	190 ± 25	185 ± 23
Ejection fraction (%)			
Rest	55 ± 6	57 ± 6	59 ± 8
Exercise	65 ± 9	67 ± 7	52 ± 6
Work load (W)	140 ± 50	120 ± 40	60 ± 35†
End-diastolic dimension (cm)			
Rest	4.5 ± 1.2	4.8 ± 0.5 (n = 13)	5.0 ± 0.6 (n = 18)
Peak filling rate (EDC/s)			
Rest	3.2 ± 0.6	2.8 ± 0.7	2.5 ± 0.8‡
Time to peak filling rate (ms)			
Rest	156 ± 19	168 ± 25	163 ± 43

* $p < 0.05$ compared with group 1.
‡ $p < 0.01$ compared with normal subjects.
† $p < 0.002$ compared with normal and group 1 subjects.
§ $p < 0.05$ compared with normal and group 1 subjects.
CAD = coronary artery disease; EDC = end-diastolic counts.

Several methods were then used to evaluate relative regional asynchrony.[4] First, the phase angle of each sector was computed in degrees, using the first harmonic Fourier expansion of the sector time-activity curve.[9] The standard deviation of the 20 sector phase values was used as an index of overall LV asynchrony.[4] Systolic asynchrony was assessed by measuring the standard deviation of the time to minimum volume for each of the 20 sectors. To improve precision and reduce errors for regional diastolic data, we created LV quadrants by combining the 20 sectors into 4 quadrants of 5 sectors each.[4] Regional time activity curves were then generated from each quadrant and were fit to a Fourier expansion with 3 harmonics. From each fitted curve, the time to peak filling rate was computed relative to each quadrant's time to minimum volume. As an index of LV diastolic asynchrony, we calculated the standard deviation of quadrant time to peak filling rate. Reproducibility of this method has been previously described.[4]

Because measurements of diastolic events are greatly influenced by heart rate and changes in ejection fraction,[10] analysis of diastolic measurements obtained during exercise is difficult. Thus, in the present study, only the resting indexes of global LV filling and regional diastolic asynchrony were considered.

Statistical analysis: All data are expressed as mean ± standard deviation of the mean. The 1-way analysis of variance was first used to assess the overall level of significance among the 3 groups. The unpaired *t* test was then used for comparisons between groups and the paired *t* test was used for comparisons within each

TABLE II Regional Left Ventricular Function

	Normal Subjects	CAD Group 1	CAD Group 2
Standard deviation of phase (degrees)			
Rest	5.4 ± 1.3	6.1 ± 1.7	6.6 ± 2.1* p <0.001
Exercise	6.3 ± 2.1	6.1 ± 3.2	9.3 ± 4.0†§
Standard deviation of time to minimal volume (ms)			
Rest	24 ± 8	24 ± 12	28 ± 10
Exercise	24 ± 7	21 ± 7	30 ± 11*§
Standard deviation of time to peak filling rate (ms)			
Rest	25 ± 16	23 ± 16	46 ± 44*‡

* p <0.05 compared with normal subjects.
† p <0.005 compared with normal subjects.
‡ p <0.05 compared with group 1 patients.
§ p <0.005 compared with group 1 patients.
CAD = coronary artery disease.

group. Chi-square analysis was performed to compare anatomic findings in the 2 groups of patients with CAD. The relations reported were analyzed by linear regression analysis. A p value <0.05 was considered throughout the study as the minimal level of statistical significance.

RESULTS

Coronary anatomy: No significant differences between the 2 CAD groups were observed either in the number of diseased vessels per patient or in the severity of coronary artery stenosis.

Global left ventricular function: At rest, there were no differences in heart rate, end-diastolic dimension and ejection fraction among the 3 groups. Systolic blood pressure was slightly but significantly higher in group 2 than in the other 2 groups of subjects (Table I). End-diastolic pressure was not significantly different between the 2 groups of coronary patients (9 ± 5 in group 1 vs 13 ± 4 mm Hg in group 2; difference not significant).

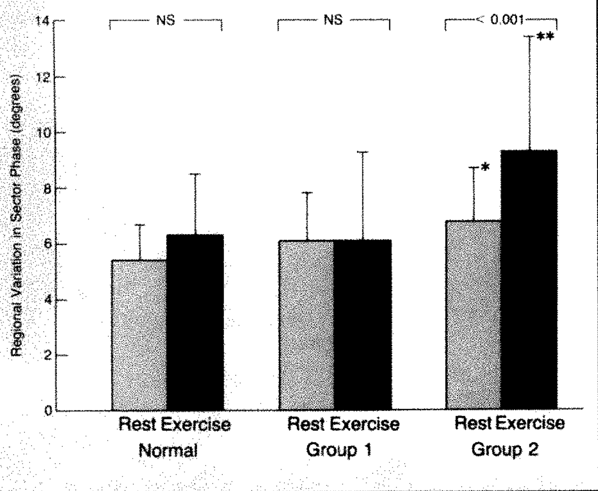

FIGURE 1. Regional variation in phase angle, measured as the standard deviation of the mean of 20 left ventricular sectors, at rest and during exercise. *p <0.05 compared with normal subjects; **p <0.005 compared with normal subjects and with group 1 patients. NS = difference not significant.

The LV ejection fraction increased during exercise in both normal subjects and in group 1 patients, whereas it decreased in group 2 patients. The decrease in ejection fraction was associated with regional wall motion abnormalities in 15 of 23 and with the occurrence of angina in 12 of 23 group 2 patients. The heart rate-pressure product achieved during exercise was significantly smaller in group 2 (20,100 ± 4,500) than in group 1 patients (23,500 ± 5,700; p <0.05) and normal subjects (23,100 ± 4,000; p <0.05). This difference was due to a lower heart rate achieved with exercise in group 2 patients as a consequence of a smaller work load (Table I).

Peak filling rate at rest was significantly lower in group 2 patients than in normal subjects (2.5 ± 0.8 vs 3.2 ± 0.6 EDC/s; p <0.01). Time to peak filling rate did not differ among groups.

Regional left ventricular function: We then assessed regional LV asynchrony (Table II). In the group of normal subjects, the standard deviation of sector phase at rest was 5.4 ± 1.3 degrees, which was similar to that observed in group 1 patients (6.1 ± 1.7 degrees; difference not significant), but significantly smaller than that observed in group 2 patients (6.6 ± 2.1 degrees; p <0.05) (Figure 1). In all CAD patients, a negative correlation was found between the resting value of the standard deviation of sector phase and global peak filling rate (r = −0.44; p = 0.002), indicating a significant association between the degree of asynchrony and diastolic filling of the ventricle. No significant differences were found in the resting values of the standard deviation of sector time to minimum volume among the 3 groups (Figure 2). However, the standard deviation of quadrant time to peak filling rate at rest was significantly higher in group 2 patients (46 ± 44 ms) than in normal subjects (25 ± 16 ms; p <0.05) and group 1 patients (23 ± 16 ms; p <0.05) (Figure 3). Thus, at rest, group 2 patients differed from the normal subjects on the basis of diastolic rather than systolic asynchrony.

Effect of systolic blood pressure in group 2: Elevated blood pressure may significantly affect LV filling.[11,12] Thus, the analysis of variables at rest was repeated after the exclusion of 3 group 2 patients with a

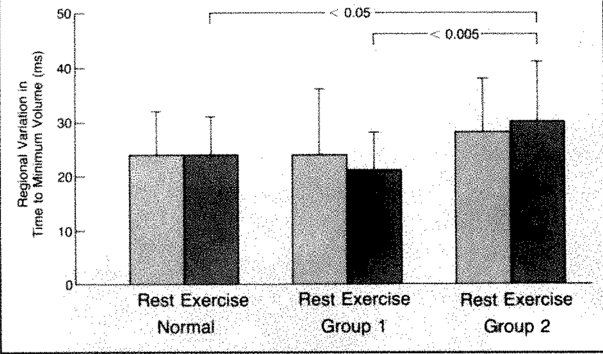

FIGURE 2. Regional variation in time to minimum volume, measured as the standard deviation of the mean of 20 left ventricular sectors, at rest and during exercise.

systolic blood pressure >160 mm Hg, at which time the mean group 2 systolic blood pressure (132 ± 9 mm Hg) was no longer significantly different from that of the other 2 groups. Repeat analysis of the resting data yielded the same results regarding impaired regional and global LV diastolic function in group 2 patients. Compared with the normal subjects, group 2 patients had a reduced global peak filling rate (3.2 ± 0.6 vs 2.5 ± 0.8 EDC/s, respectively; $p < 0.01$) and greater diastolic asynchrony (25 ± 16 vs 50 ± 46 ms, respectively; $p < 0.05$).

Regional asynchrony during exercise: With exercise, the standard deviation of phase increased significantly in group 2 patients (from 6.6 ± 2.1 to 9.3 ± 4 degrees; $p < 0.001$). This value was also significantly greater than in the other 2 groups (Figure 1). In group 2 patients, the increase in the standard deviation of sector phase with exercise correlated significantly ($r = -0.54$; $p < 0.01$) with the magnitude of the abnormal ejection fraction response. In addition, systolic dyssynchrony in group 2 patients during exercise was significantly increased compared with that in both group 1 and normal subjects, as manifested by a greater variation in regional time to minimum volume (Figure 2).

DISCUSSION

In the present study, we assessed LV filling characteristics in 2 groups of patients with CAD, both with normal systolic function at rest and a similar degree and severity of CAD, who differed with respect to the ejection fraction response to exercise. Neither group had evidence of systolic asynchrony at rest, reflecting our selection criterion of normal regional wall motion by visual analysis. However, only the patient subgroup with an abnormal exercise response showed reduced global peak filling rate and increased diastolic asynchrony at rest.

Left ventricular asynchrony at rest: LV asynchrony has been experimentally[13-17] and clinically[18] reported to impair LV function. In particular, asynchronous regional function at rest in patients with CAD has been previously reported and related to the impairment of global diastolic function,[3,4] a finding confirmed in the present study. Despite some overlap among the 3 groups, the degree of diastolic asynchrony at rest was significantly higher in the group of patients with exercise-induced LV dysfunction: this suggests that diastolic asynchrony at rest and the associated impairment of global ventricular filling, in the absence of previous infarction or clinically overt ischemia at rest, reflect a greater functional severity of coronary disease. It seems unlikely that different loading conditions among the 3 groups would explain the differences in regional and global diastolic function, because end-diastolic dimension was similar among the 3 groups and the end-diastolic pressure was not significantly different between the 2 groups of CAD patients. Moreover, the same differences in diastolic function between the 2 groups of patients with CAD were observed when they were matched for systolic blood pressure values.

Mechanisms of left ventricular asynchrony at rest: The mechanisms responsible for regional LV asynchrony are still not completely understood. Recent evidence from myocardial biopsy specimens suggests that asynchronous LV function might result from regional morphologic changes arising from recurrent episodes of myocardial ischemia.[19] However, the reversal of asynchronous function in many patients with revascularization[4,20] would argue in favor of a reversible rather than a fixed structural process.

The loss of the "erectile effect" related to diastolic coronary blood flow has been proposed[2] to explain diastolic asynchrony at rest, because rapid filling of the coronary bed in early diastole may be an important mechanical determinant of LV relaxation. However, we believe that subclinical ischemia is the most likely explanation for our observations, as supported by several experimental and clinical studies.[21-25] The experimental findings of prolongation of developed tension during recovery from hypoxia[26] and incomplete relaxation between beats during hypoxia and tachycardia,[27] observed even at rest in patients with CAD and exercise-induced ischemia,[28] could translate clinically into nonuniformity of LV contraction and relaxation. An additional consideration is that myocardial ischemia may increase the physiologic degree of nonuniform adrenergic function within the left ventricle.[29,30]

Left ventricular asynchrony with exercise: Our data also demonstrate a relation during exercise between the development of regional systolic asynchrony and global changes in systolic function. Only patients with exercise-induced systolic dysfunction showed a significant

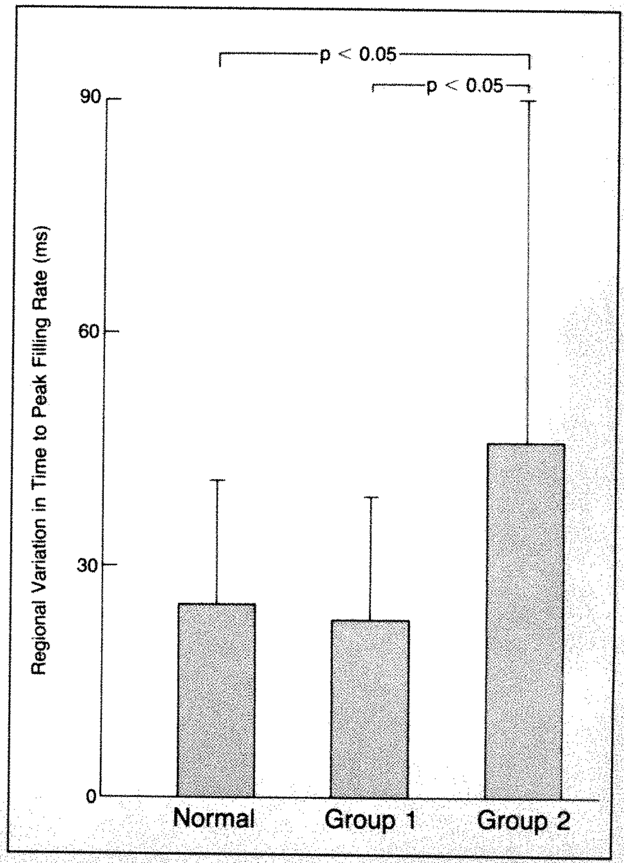

FIGURE 3. Regional variation in time to peak filling rate, measured as the standard deviation of the mean of 4 left ventricular quadrants at rest in the 3 groups.

increase in systolic asynchrony, and the systolic asynchrony was linearly related to the degree of systolic dysfunction, suggesting a cause-effect relation. Thus, exercise-induced ischemia may produce regional dysfunction and asynchrony, the magnitude of which determines the change in global systolic function.

Study limitations: In the present study, neither coronary blood flow nor lactate metabolism was measured. Thus, some degree of ischemia during exercise could have been present in the group of patients with normal exercise responses. Moreover, the extent of CAD was only qualitatively assessed in our study. Thus, we cannot rule out the possibility that a more quantitative analysis of the coronary angiograms would have shown a different degree of coronary disease between the 2 groups of patients. Finally, the slight but significant age difference between the 2 groups of coronary patients could also account for some of the differences observed in regional and global diastolic function. However, the patients with an abnormal ejection fraction response did not differ in age from the normal subjects, indicating that the difference in age cannot be solely responsible for the regional and global abnormalities of LV function in this group of patients.

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The Dutch Experience in Percutaneous Transluminal Angioplasty of Narrowed Saphenous Veins Used for Aortocoronary Arterial Bypass

H. W. Thijs Plokker, MD, PhD, B. Hannie Meester, MD, and Patrick W. Serruys, MD, PhD

Of 19,994 percutaneous transluminal coronary angioplasty procedures performed in The Netherlands between April 1980 and January 1989, the long-term follow-up of 454 patients who underwent angioplasty of ≥1 saphenous vein bypass graft was reviewed. In 46% of patients single graft angioplasty was attempted, and in 54% of patients sequential graft angioplasty was attempted. The clinical primary success rate was 90%. In-hospital mortality was 0.7%, 2.8% of patients sustained a procedural myocardial infarction, and 1.3% of patients underwent emergency bypass surgery. After a follow-up period of 5 years, 74% of patients were alive, and 26% were alive and event-free (no myocardial infarction, no repeat bypass surgery or repeat angioplasty). In patients in whom the initial angioplasty attempt was unsuccessful, only 3% were event-free at 5 years, versus 27% of successfully dilated patients. The time interval between the angioplasty attempt and previous surgery was a significant predictor for 5-year event-free survival. The event-free survival rates for patients who had bypass surgery 1 year before, between 1 and 5 years, and 5 years before angioplasty, were 45, 25 and 19%, respectively. Less than one-third of patients with previous bypass surgery who had angioplasty of the graft remained event-free after 5 years. In patients needing angioplasty within 1 year after bypass surgery, better long-term results were achieved.

(Am J Cardiol 1991;67:361–366)

Recurrence of angina pectoris after aortocoronary bypass surgery in patients with coronary artery disease is either caused by progression of disease in the native coronary artery or by the development of new narrowings in ≥1 bypass graft. Because of the increased morbidity and mortality of coronary reoperations, it is not surprising that percutaneous transluminal balloon angioplasty has been attempted in such patients to prevent a reoperation. It has been demonstrated[1–9] that angioplasty can be successfully performed in patients with a hemodynamically significant stenosis in a venous coronary bypass graft. Little is known about the long-term outcome after angioplasty.[8,10] In this study, we evaluated the long-term clinical effects of balloon angioplasty in venous bypass grafts in all 454 patients who had undergone such a procedure in The Netherlands between April 1980 (when the first coronary angioplasty procedure was performed) and January 1989. During this time period, a total of 19,994 coronary angioplasty procedures were performed in the country, of which the 454 patients represent 2.7%.

METHODS

Between April 1980 and January 1989, 454 patients underwent angioplasty of at least 1 stenosis of >50% diameter in ≥1 saphenous vein bypass graft. Two hundred and sixty-four of 454 patients (58.1%) underwent an angioplasty either of the bypass graft and ≥1 native vessel (38 patients, 14.4%) or of the bypass graft alone (226 patients, 85.6%). There were 368 men (81%) and 86 women (19%) aged 34 to 78 years (mean ± standard deviation 60 ± 8.4). The number of diseased vessels was known for 200 of the 454 patients (44.1%). One-vessel disease was reported in 15 of 200 patients (7.5%), 2-vessel disease in 36 patients (18%) and 3-vessel disease in 149 patients (74.5%). In 46% of patients ≥1 stenoses in ≥1 single graft were dilated, and in 54% of patients ≥1 stenoses in a sequential or jump graft were dilated. In the patients who underwent single graft angioplasty, dilatation was attempted in 69% in grafts to the left anterior descending artery, in 21% in grafts to the right coronary artery and in 10% in grafts to the circumflex artery. The interval between coronary artery bypass surgery and balloon dilatation (or "graft age") ranged from 6 months to 17 years (mean age 5.7 ± 3.8 years) (Figure 1).

Primary success was defined as a reduction of the diameter stenosis to ≤50%, without the occurrence of

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See Appendix for participating centers and institutions.

an acute myocardial infarction, emergency bypass surgery or death, during the hospital stay of the patients. Acute myocardial infarction was defined as the occurrence of new Q waves on the electrocardiogram ≥30 ms or an increase in creatine phosphokinase to >3 times normal. Aortocoronary bypass surgery was considered to be an emergency when the patient was immediately transferred from the cardiac catheterization laboratory to the operating room.

Follow-up data were first obtained by means of a letter to the Civil Registration Service to establish survival status. If the patients were alive, they were interviewed by telephone, written questionnaires or outpatient clinic visits. The following events were considered as clinical end points: death, acute myocardial infarction, reoperation and redilatation.

All data are presented as mean ± 1 standard deviation. Life tables were actuarially calculated according to the Kaplan-Meier method. The generalized Wilcoxon test was performed to detect differences between the subgroups. A p value <0.05 was considered statistically significant.

RESULTS

The primary success rate was 90%. In-hospital mortality was 0.7%. In 2.8% of patients there was evidence of a procedural acute myocardial infarction. In 1.3% of patients emergency coronary artery bypass surgery was performed.

Actuarial survival for the entire group was 74% (±3.4%) at 5 years (Figure 2) and 63% (±8%) at 8 years. However, in patients with initial unsuccessful graft angioplasty, 58% were alive at 5 years versus 78% of patients in whom graft angioplasty was successful (p <0.001) (Figure 3).

After a follow-up period of 5 years, 58% of patients were alive and did not sustain a myocardial infarction. Thirty-four percent were alive, had no evidence of a myocardial infarction, and did not undergo repeat bypass surgery. After these 5 years 26% of patients

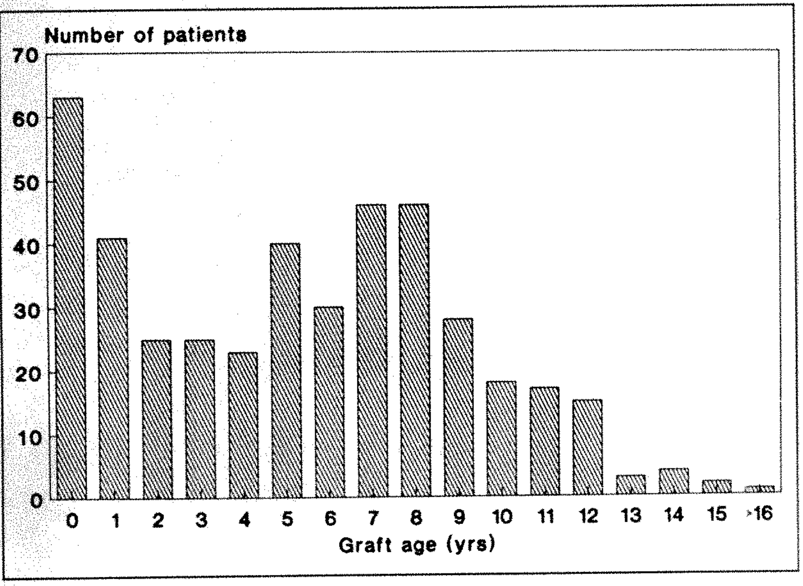

FIGURE 1. The time interval between graft angioplasty and previous surgery ("graftage") ranged from 6 months to 17 years (mean age 5.7 ± 3.8 years).

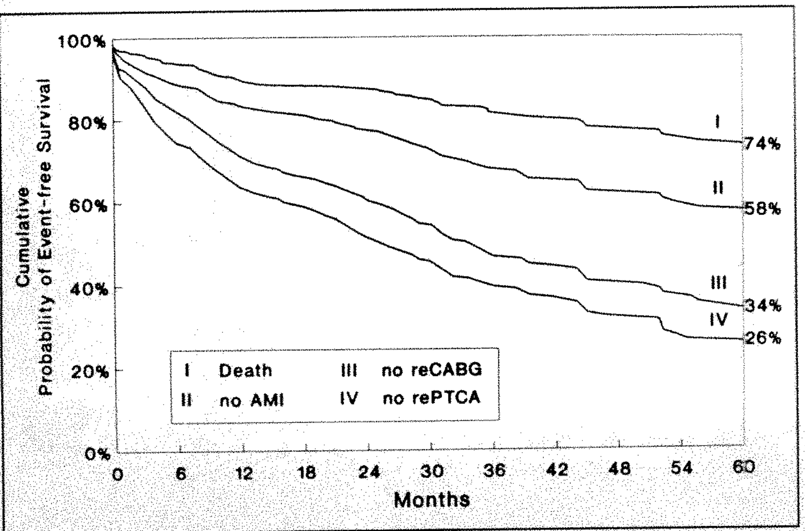

FIGURE 2. After the follow-up period of 5 years, the cumulative probability of survival without any cardiac event (death, myocardial infarction, repeat bypass surgery and repeat angioplasty) was 26% (±3.3%) for all 454 patients. AMI = acute myocardial infarction; reCABG = repeat coronary artery bypass grafting; rePTCA = repeat percutaneous transluminal coronary angioplasty.

(±3.3%) were alive and event-free. When only death, myocardial infarction and reoperation were considered as clinical end points, 34% of patients were alive and event-free after 5 years (Figure 2).

In patients in whom the initial graft angioplasty attempt was unsuccessful, only 3% were event-free at 5 years, versus 27% event-free patients in whom initial graft angioplasty was successful ($p < 0.0001$) (Figure 4). When grouped by graft age (intervals between bypass surgery and angioplasty <1 year, between 1 and 5 years, and ≥5 years), there were statistically significant differences in 5-year event-free survival rates, namely 45% for patients who underwent angioplasty within 1 year after bypass surgery, in contrast to 25 and 19% for patients with grafts that had been implanted between 1 and 5 years, and >5 years before angioplasty, respectively ($p < 0.005$) (Figure 5).

DISCUSSION

Between April 1980 and January 1989, 19,994 angioplasty procedures were performed in The Netherlands. In this large collected angioplasty experience, only 2.7% of procedures included vein graft dilatation. Many contemporary series have a larger number of patients with graft dilatation. However, our reported incidence of 2.7% is a cumulative number and does not reflect the current percentage of patients undergoing graft angioplasty in The Netherlands, which was 4.1% in 1988. In 1988 the percentage of patients with previous bypass surgery undergoing angioplasty of the graft or ≥1 more native vessel, or both, was 10.3%.

Furthermore, between 1980 and 1989 there has been a progressive recruitment of centers. The number of catheterization laboratories performing angioplasty in the country increased from 5 to 12. In addition, the expansion of the indication of graft angioplasty has been a slowly evolving phenomenon, which is also shown by the high incidence of bypass operations in The Netherlands.

Recurrence of angina after coronary artery bypass grafting remains a major clinical problem. Failure of aortocoronary saphenous vein bypass grafts is generally the result of either vein graft stenosis or progressive ath-

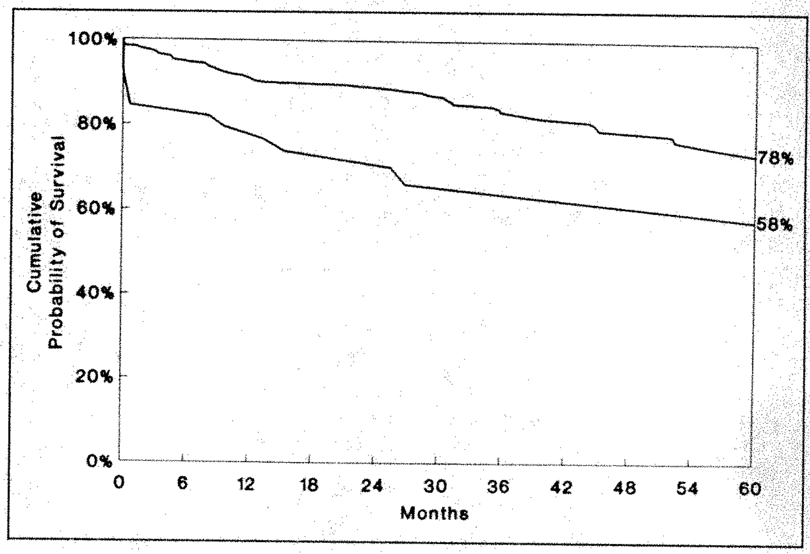

FIGURE 3. The cumulative probability of 5-year survival grouped by success. In patients in whom graft angioplasty had been unsuccessful, the probability of survival was significantly lower (58%) than in those in whom graft angioplasty had been successful (78%) ($p < 0.001$).

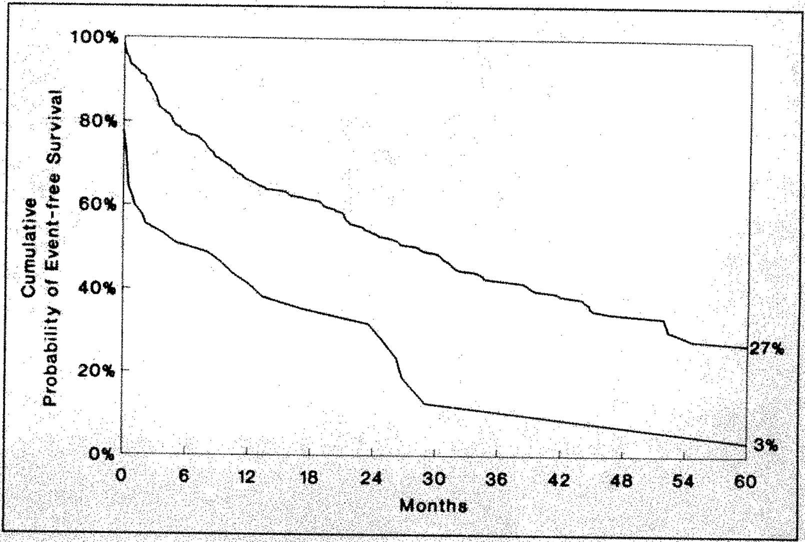

FIGURE 4. The cumulative probability of 5-year event-free survival grouped by success. In patients in whom the initial graft angioplasty attempt had been unsuccessful, the chance of remaining event-free for the first 5 years after the procedure was as low as 3%, compared with 27% for those in whom graft angioplasty had been successful ($p < 0.0001$).

TABLE I Success of Saphenous Vein Graft Angioplasty Compared with Pooled Data from 14 Series

Year	Authors	No. of SVG PTCAs	No. of Successes (%)
1981	Ford et al[24]	9	89
1983	Douglas et al[1]	62	94
1984	Block et al[2]	40	78
	Dorros et al[8]	33	79
	El Gamal et al[29]	44	93
1985	Corbelli et al[3]	47	91
	Marquis et al[4]	24	79
	Slysh et al[5]	6	100
1986	Reeder et al[6]	19	84
1987	Cote et al[7]	88	86
	Ernst et al[10]	33	97
	Pop et al[30]	49	74
1988	Dorros et al[12]	53	83
	Pinkerton et al[9]	100	93
	Overall	607	87

PTCA = percutaneous transluminal coronary angioplasty; SVG = saphenous vein graft.

erosclerotic narrowing of distal native coronary arteries. Symptoms of myocardial ischemia will recur or progress in about 5% of patients per year.[11,12] Early graft narrowing occurs in up to 10% of grafts within 1 to 2 weeks after the operation and 15 to 20% by 1 year.[13-15] After 5 years, up to 25% of grafts are occluded, whereas 52% may show stenoses of >70%.[15] Stenosis within the first month is almost always due to thrombosis and is generally related to technical factors such as anastomotic narrowing, operative trauma to the vein graft and inadequate distal runoff.[12] It has been demonstrated that between 1 month and 1 year postoperatively, intimal fibromuscular proliferation is the most prevalent form of obstruction. Postoperatively, beyond 1 year and particularly after 3 years, atherosclerosis becomes an important cause of vein graft stenosis and may coexist with fibromuscular proliferation.

Plaques in vein grafts resemble those in native coronary arteries and are generally soft and friable rather than densely fibrotic or calcific. Furthermore, because vein grafts tend to be larger than the native coronary arteries to which they are anastomosed, and because vein graft atherosclerosis often occurs in aneurysmally dilated segments, the plaques are generally quite large relative to those in native coronary arteries. Accordingly, atherosclerotic plaques in vein grafts seem particularly vulnerable to disruption and to embolization of relatively large fragments.

Although coronary artery bypass surgery using internal mammary artery grafts gives much better long-term graft patency rates,[7-9,16] vein grafts will continue to be utilized in a majority of surgical candidates with multivessel coronary artery disease, because not all vessels can be bypassed using internal mammary conduits.

Reoperation is technically more complicated to perform and is generally associated with a higher morbidity and mortality than a primary operation, and achieves symptomatic relief in only 60 to 70% of patients, compared with the 80 to 90% success rate after primary operations. The perioperative myocardial infarction rate varies among surgical groups from 2.0 to 11.5%. The mortality rate after repeat bypass surgery varies from 1.2 to 12.5%, and the incidence of reoperation for bleeding ranges from 3.6 to 10.2%.[17-23]

Angioplasty of a saphenous vein bypass graft was first performed in 1978 by Ford.[24] Since then a number of publications have shown the feasibility of this technique, with an overall success rate of 87% (Table I). Almost the same success rate was seen in our combined Dutch series. These rather high success rates probably reflect careful patient selection. Long midgraft lesions with highly irregular borders were usually avoided because of the risk of distal embolization from detached material within the grafts, but our angiographic data are insufficient to further detail the angiographic appearance of the lesions before percutaneous transluminal coronary angioplasty.

After a follow-up period of 5 years, 74% of 454 patients were alive, and only 26% of patients were alive and event-free. The number of diseased vessels was

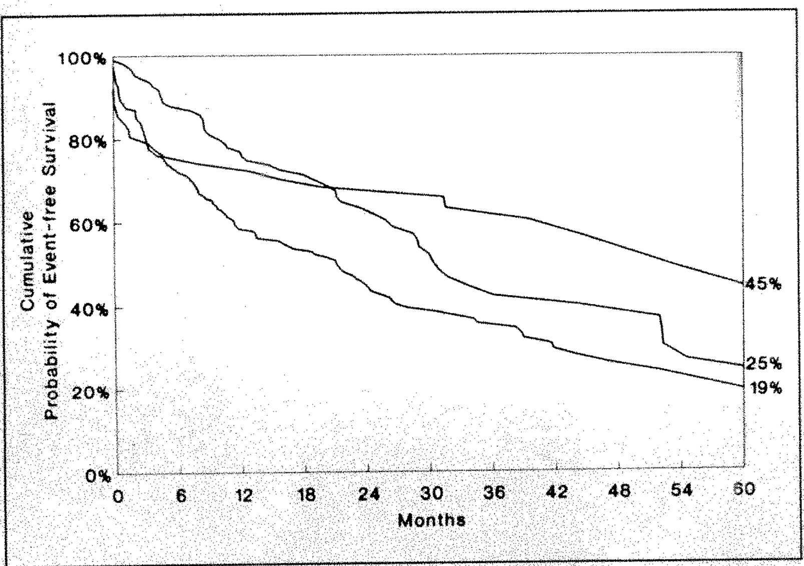

FIGURE 5. The cumulative probability of survival at 5 years grouped by graftage (intervals between coronary artery bypass grafting and angioplasty <1 year, between 1 and 5 years, and ≥5 years). The differences in 5-year event-free survival rates were statistically significant: 45% for patients who underwent angioplasty within 1 year after surgery, compared with 25 and 19% for patients with grafts that had been implanted between 1 and 5 years, and at ≥5 years before angioplasty (p <0.005).

known for 44.1% of patients, so we could not ascertain the presence of multivessel disease as a factor leading to late events and reinterventions in the follow-up of these patients. Since, in this survey type of investigation, the reason for late events or repeat angioplasty or repeat bypass surgery is not available, it is difficult to speculate on the physiopathologic mechanism responsible for these follow-up events. We can not be certain if graft restenosis plays a major role in the high incidence of late events.

However, the interval between coronary artery bypass surgery and angioplasty was known in all our patients (Figure 1). There were statistically significant ($p < 0.05$) differences in event-free survival rates after a follow-up period of 5 years among patients who underwent bypass surgery within 1 year before angioplasty, between 1 and 5 years, and >5 years before angioplasty. Event-free survival was reported in 45, 25, and 19% of patients, respectively. This finding is in agreement with previously published data[1-3,7-9,12] that suggest that anastomotic lesions respond better to angioplasty than lesions that occur later (midgraft). The manner in which balloon angioplasty relieves obstructions in vein grafts appears to be similar to that described for native coronary arteries and is characterized primarily by intimal tears and plaque disruption. Within the first postoperative month, balloon angioplasty may be beneficial to relieve stenoses, particularly at distal anastomosis sites. Angioplasty of aortocoronary saphenous vein bypass grafts >1 year of age can be performed with the realization that involvement by friable atherosclerosis is likely and that atheroembolization represents a risk.[25,26]

Eventually, the higher risk of reoperation will make the use of less aggressive forms of therapy more attractive. Angioplasty of the venous conduits, of the native vessels themselves and alternative forms of nonsurgical revascularization such as atherectomy, stenting and laser (balloon) angioplasty may obviate repeat bypass surgery in some patients.[27,28] However, within the limits of our study, we have not been able to look at the results of angioplasty of native coronary arteries in patients who again become symptomatic after venous bypass graft procedures. From published reports it seems that this technique also has its limitations.[1,3,10,12]

Our data demonstrate that 74% of patients who undergo angioplasty of a stenosis in a venous graft survive 5 years after the angioplasty procedure, and that only 26% remain free of any major event. However, in patients needing angioplasty within 1 year after bypass surgery, better long-term results can be achieved. Finally, angioplasty of a venous graft stenosis may be an alternative to reoperation in some patients with previous coronary artery bypass surgery.

It is the inherent limitation of this type of epidemiologic historical survey, that, although it provides the clinical investigator with large numbers, the nonprospective nature of this investigation does not permit one to identify the factors that may improve patient selection.

Acknowledgment: We thank Ed van de Berge (CADANS/ICIN) and Piet Jonkers (Thoraxcenter) for their great help in data acquisition and data processing.

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APPENDIX

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Predictors of Cardiac Survival After Percutaneous Transluminal Coronary Angioplasty in Patients with Severe Left Ventricular Dysfunction

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To assess the outcome of percutaneous transluminal coronary angioplasty (PTCA) in patients with severe left ventricular (LV) dysfunction and to determine the predictors of mortality, 73 patients with LV ejection fraction ≤40% who underwent initial PTCA were analyzed. The majority of patients had prior (>1 week) myocardial infarction (62 patients, 85%). Congestive heart failure and unstable angina were present in 24 (45%) and 49 (67%) patients, respectively. Multivessel coronary artery disease was present in 60 (83%). The LV ejection fraction ranged from 14 to 40% (mean 34%). Intraaortic balloon pump (15%) and percutaneous cardiopulmonary bypass support (4%) was used infrequently. Angiographic success was obtained in 109 of 128 lesions (85%) attempted. Complete revascularization was obtained in 16 of 60 patients with clinical success. Procedure-related mortality was 5% (4 patients). All patients were followed from ≥6 to ≤71 months (average 26).

The estimated survival was 79 ± 5%, 74 ± 6%, 66 ± 7% and 57 ± 8% at 1, 2, 3 and 4 years, respectively. A Cox regression analysis revealed that the presence of congestive heart failure, a lower LV ejection fraction and a higher myocardial jeopardy score for contractile myocardium were independent predictors of survival after PTCA in patients with LV dysfunction. In conclusion, a high-risk subset can be identified among patients with severe LV dysfunction who undergo PTCA.

(Am J Cardiol 1991;67:367–372)

Left ventricular (LV) function is the most important determinant of survival in patients with coronary artery disease (CAD).[1] Despite increased operative mortality, the overall survival of selected patients with CAD and severe LV dysfunction can be improved with coronary artery bypass graft revascularization compared with medical treatment.[2-5]

The role of percutaneous transluminal coronary angioplasty (PTCA) in the treatment of CAD patients with LV dysfunction has not been well defined.[6-8] Successfully performed PTCA brings an immediate increase in reversibly depressed LV regional systolic function,[9,10] which persists unless severe restenosis develops.[11] With increasing application of PTCA in patients with multivessel CAD,[12] a potentially larger number of patients with decreased LV function will be considered as candidates for the procedure. This broadening application may also include patients undergoing PTCA for the treatment of acute myocardial infarction, a condition associated with varying degrees of LV dysfunction.[13]

This report assesses the immediate and short-term outcome in patients with severe LV dysfunction and identifies the clinical, angiographic and procedural predictors of cardiac survival after the procedure.

METHODS

Study group: Of 2,118 consecutive patients who underwent a first coronary angioplasty at St. Louis University from May 1983 to February 1989, 73 consecutive patients (3.4%) with LV ejection fractions ≤40% comprised the study group. Patients with acute transmural myocardial infarction within 1 week before PTCA were excluded. Patients without left ventriculograms were also excluded. In our clinical practice, the patients were not denied PTCA on the basis of left ventricular dysfunction. However, patients with narrowings at a very high-risk location (e.g., left main coronary artery) or those with unfavorable characteristics of narrowings (e.g., long, chronic total occlusion, lesion length >2 cm, heavy calcification, bend >45° angle) were not always considered for PTCA.

Cardiac catheterization: Selective right and left coronary angiography was performed in multiple views, including craniocaudal and caudal-cranial angular views. Single-plane left ventriculography was performed in the 30° right anterior oblique view. Left anterior oblique

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left ventriculograms were not performed in most patients. Therefore, only a single-plane left ventriculogram was analyzed. Ejection fractions were determined by the area-length method. Coronary narrowings were measured in 2 views using electronic calipers and expressed as percent diameter narrowing compared with the diameter of the nearest normal arterial segment. The average of both views determined the percent reduction in luminal diameter. A ≥50% average narrowing was accepted as significant. The extent of coronary disease and the left ventricular contraction score were classified according to the Coronary Artery Surgery Study coding system.[14] Major coronary arteries were defined as the left anterior descending and its large diagonal branches, the left circumflex and its large obtuse marginal branches and a balanced or dominant right coronary artery. Multivessel disease was defined as an average stenosis ≥50% of ≥2 major coronary arteries. The presence or absence of collaterals were noted for each arterial territory.

Myocardial territory score: Myocardial territory score was determined according to modification of the method of Alderman et al.[15] The relative size of myocardial territory supplied by the terminal branches of the coronary tree (e.g., distal left anterior descending, obtuse marginal branch) was scored as small, medium or large in the following manner:

A *large* territory was subtended by a terminal branch extending ≥⅔ of the distance from base to apex of the left ventricle in a projection which best elongates the segment.

A *medium* territory was subtended by a terminal branch extending from ¼ to ⅔ the base-to-apex length.

A *small* territory was subtended by a terminal branch extending <¼ the base-to-apex length.

Sizing the distal left anterior descending artery (LAD) was unique: A small distal LAD terminated before the apex; a medium LAD at the apex; and a large LAD wrapped around the apex of the left ventricle. A point value of 3 was assigned for each large branch, 2 for each medium branch and 1 for each small branch. The total LAD septal territory was always given a score of 3 points. A myocardial jeopardy score was then defined as a measure of potentially ischemic myocardium. The myocardial jeopardy score was calculated by dividing the sum of branches distal to a stenosis ≥50% by the sum of all branches. A modified jeopardy score for contractile myocardium was also calculated similarly by assuming a zero jeopardy score value for an akinetic territory supplied by a vessel with ≥50% stenosis. The myocardial jeopardy score was calculated before and after PTCA after retrospective review of all cineangiograms by 2 reviewers unaware of clinical outcome.

Percutaneous transluminal coronary angioplasty: PTCA was performed by means of standard techniques and a steerable balloon catheter system. Dilatation of the culprit lesion was attempted first, followed by revascularization of other major vessel territories when necessary. If the culprit lesion was not successfully dilated, the procedure was terminated. A functional rather than anatomic complete revascularization was targeted. Accordingly, a lesion on a vessel supplying a chronically akinetic area was not routinely attempted, except for providing a potential collateral source. Patients routinely underwent anticoagulation with a bolus of 10,000 units of intravenous heparin during the procedure. Additional heparin was administered if the procedure was prolonged. The heparin infusion (1,000 units/hour) was maintained overnight or longer in patients who had angiographic evidence of a large intimal tear or dissection. Calcium antagonists and antiplatelet drug therapy (325 mg of aspirin and 75 mg of persantine administered 3 times daily) were begun before the procedure. Percutaneous cardiopulmonary bypass and intraaortic balloon pumping were used in 3 (4%) and 11 (15%) patients, respectively. The indication for percutaneous cardiopulmonary bypass was either dilatation of a vessel supplying >50% of the myocardium or dilatation of the only remaining vessel. The indications for intraaortic balloon pumping were cardiogenic shock, unstable angina and dilatation of a vessel supplying an extensive area of myocardium as previously described.

An angiographic success was defined when ≥30% reduction in the luminal diameter of the stenosis was obtained and the residual narrowing was <50%.

A clinical success was defined as successful dilatation of at least the culprit lesion, with immediate clinical improvement in anginal status without major in-hospital complications such as myocardial infarction, the need for emergency coronary bypass grafting or death.

Degree of revascularization: Revascularization was considered complete where all major coronary or branch vessel lesions ≥50% were successfully dilated. This was equal to a post-PTCA jeopardy score of 0.

Functional evaluation and follow-up: All patients were eligible for ≥6 months follow-up. Follow-up functional status and presence or absence of cardiac events or complications were determined by clinical visits, telephone interview and periodic questionnaires. All deaths that occurred as a result of clearly described noncardiac causes (such as cancer, accidents) were classified as noncardiac deaths and the remaining deaths were accepted as cardiac deaths. No verification of cause of death was attempted other than available records and family's description.

Data collection and entry: Demographic and clinical information, angiographic and angioplasty measurements and data after angioplasty were recorded on standard forms by a physician prospectively during hospitalization. This information was audited for completeness and entered into a computerized data bank.

Statistical analysis: The survival was estimated by the Kaplan-Meier method. The baseline, clinical and angiographic factors listed in Tables I and II were analyzed using a Cox proportional-hazards regression program (BMDP) with regard to cardiac mortality after PTCA.[16] Relative risk ratios were calculated from estimated risks for favorable and unfavorable values of each independent variable.[17] A p (2-tailed) value <0.05 was considered statistically significant.

RESULTS

The clinical and angiographic features of patients are listed in Tables I and II, respectively.

TABLE I Clinical Description of 73 Patients with Severe Left Ventricular Dysfunction Who Underwent Coronary Angioplasty

Characteristics	No. of Pts.	%
Total	73	
Age (yr), mean (range)	62 ± 10	(36–82)
Men	53	73
Unstable angina*	49	67
Prior MI (>3 months)	30	42
Recent Q-wave MI (≤3 months but >1 week)	14	19
Non-Q-wave MI	18	25
No recent or prior MI	11	15
History of CHF	33	45
Diabetes mellitus	20	27

* National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry definition.
CABG = coronary artery bypass grafting; CHF = congestive heart failure; MI = myocardial infarction.

TABLE II Angiographic Characteristics of 73 Patients with Severe Left Ventricular Dysfunction Who Underwent Coronary Angioplasty

Characteristics	No. of Pts	%
One-vessel disease	13	18
Two-vessel disease	36	49
Three-vessel disease	24	33
Mitral regurgitation		
No	60	82
<3+	10	14
≥3+	3	4
Ejection fraction (%), mean (range)	34 ± 6	(14–40)
Left ventricular score, mean (range)	14 ± 3	(8–21)
Baseline (mean, range)		
Global jeopardy score	0.62 ± 0.21	(0.22–1.0)
Jeopardy score for contractile myocardium	0.38 ± 0.25	(0.0–1.0)
Post-PTCA (mean, range)		
Global jeopardy score	0.31 ± 0.24	(0.0–0.95)
Jeopardy score for contractile myocardium	0.18 ± 0.22	(0.0–0.91)

PTCA = percutaneous transluminal coronary angioplasty.

Primary success and acute complication: Angiographic success was accomplished in 85% of the 128 lesions attempted in the 73 patients. The global jeopardy score was decreased significantly from 0.62 ± 0.21 (range 0.22 to 1.0) to 0.31 ± 0.24 (range 0 to 0.95) after PTCA. Clinical success was achieved in 60 patients (82%). The clinical success tended to be higher in patients with 1 rather than in those with 2- or 3-vessel disease (92, 86 and 71%, respectively, $p < 0.25$). Of the 60 patients with clinical success, 16 (27%) had complete revascularization. The incomplete revascularization was due to residual total occlusions in 30 (68%), 70 to 99% narrowings in 11 (25%) and 50 to 69% narrowings in 3 patients (7%). The jeopardy score after PTCA in this group was 0.33 ± 0.15. There were 5 patients (7%) with serious procedure-related complications; 3 had Q-wave myocardial infarction: 2 died, 1 after CABG; 1 had acute closure requiring emergency coronary artery bypass grafting and 1 additional patient's death was related to acute closure.

Three patients without procedural complications underwent coronary artery bypass surgery before hospital discharge. In 2 of these, PTCA was unsuccessful and, in 1, although the PTCA was initially successful, only incomplete revascularization was obtained.

In-hospital mortality: Besides the 3 deaths as a result of PTCA complications, there was 1 other in-hospital death. This patient had an angiographically successful result with no clinical or electrocardiographic evidence of reocclusion and died suddenly (PTCA site was open at autopsy). Therefore, the total in-hospital mortality was 5% in 73 patients.

Follow-up: All surviving patients were followed from ≥6 to ≤71 months (mean 26) after PTCA. Estimated survival was 79 ± 5% (n = 46), 74 ± 6% (n = 33), 66 ± 7% (n = 18) and 57 ± 8% (n = 12) at 1, 2, 3 and 4 years, respectively (Figure 1). The following nonfatal events were noted in patients during follow-up: nonfatal myocardial infarction—3 patients (4%), coronary bypass surgery—5 patients (7%), repeat PTCA—3 patients (4%).

According to Cox regression analysis (Table III), the predictors of cardiac mortality in this series of patients were the presence of congestive heart failure ($p = 0.002$), low LV ejection fraction ($p = 0.027$) and high-baseline jeopardy score for contractile myocardium ($p = 0.035$). When the latter was kept out of the model, the baseline global jeopardy score was marginally related to outcome ($p = 0.06$). Estimated survival curves for the presence or absence of these variables is shown in Figure 2.

DISCUSSION

In this series of patients with relatively high-risk features, PTCA was clinically successful in 82%, with a 3% emergency coronary artery bypass surgery and a 4% acute myocardial infarction rate. Procedure-related death was observed in 4% of our patients with a total in-hospital mortality of 5%. The comparative data on the results of PTCA in patients with LV dysfunction are scarce. The current clinical selection process in most centers for PTCA excludes most patients with severe

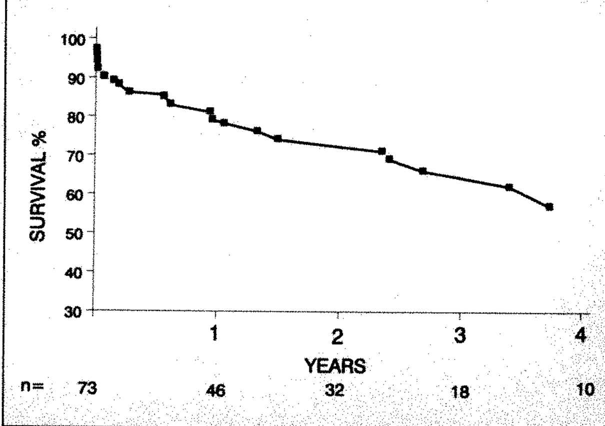


FIGURE 1. Kaplan-Meier estimated survival after percutaneous transluminal coronary angioplasty in patients with left ventricular dysfunction. *Bottom,* number of patients at risk of death at each interval.

TABLE III Results of Cox Regression Analysis

Independent Variable	Regression Coefficient	Standard Error	Favorable/ Unfavorable*	Relative Risk	Ratio of Risks	p†
Congestive heart failure	1.068	0.501	0	0.6	3.0	0.002
			1	1.8		
LV ejection fraction	−0.078	0.034	40	0.6	3.3	0.027
			25	2.0		
Jeopardy score for contractile myocardium	2.149	0.821	0.25	0.5	1.6	0.035
			0.50	1.3		

* Arbitrarily defined for left ventricular ejection fraction and jeopardy score.
† Improvement in chi-square.
LV = left ventricular.

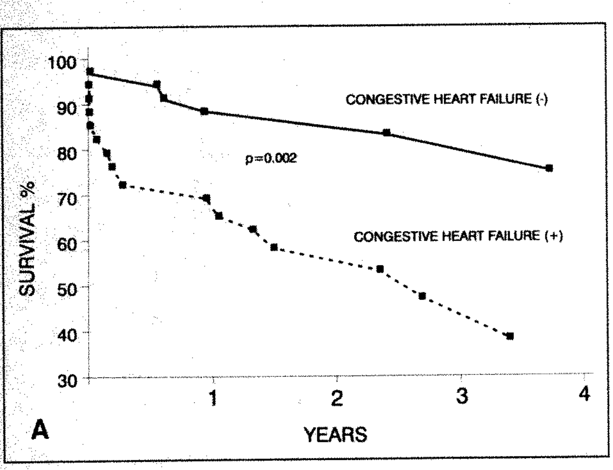
LV dysfunction because of unsuitable total occlusions or high-risk coronary anatomy.

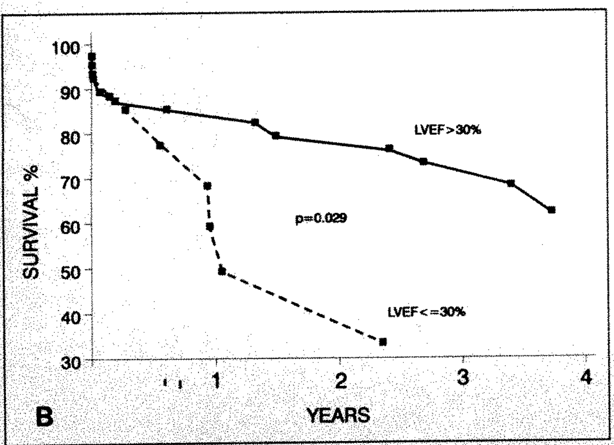
Hartzler et al[6] reported their experience with "high-risk" PTCA in several patient subsets with unfavorable features. Among the 664 patients with ejection fraction ≤40%, the procedure-related mortality was 2.7% with a relative risk ratio of 5.9. With the exception of acute myocardial infarction and left main dilatations, poor LV function had the highest risk ratio among the other high-risk factors, including age ≥70 years, left main equivalent disease, 3-vessel dilatation and unstable angina.

In a preliminary report, Dorros et al[7] reported PTCA results in 101 patients with LV ejection fraction ≤35%. The success rate in this study was 86% with 4% mortality, 4% acute myocardial infarction and 3% emergency coronary bypass surgery rates, comparable to our results. Although these investigators did not report the extent of CAD, 45% of their patients had undergone coronary artery bypass grafting and 81% had prior myocardial infarction.

Kohli et al[8] performed PTCA in 63 patients with LV ejection fraction ≤35%. This series included 40% with recent myocardial infarction, 69% with unstable angina and 74% with multivessel coronary artery disease. These investigators reported a clinical success rate of 90% with an acute complication rate comparable to our study (7% acute myocardial infarction rate and 3.3% mortality).

Supported percutaneous transluminal coronary angioplasty and mortality: These immediate results suggest that in patients with LV dysfunction who undergo PTCA, procedure-related mortality is increased. The intraaortic balloon pump[18] and, recently, percutaneous cardiopulmonary bypass[19] have been used to increase the safety of PTCA in patients with LV dysfunction. In our series, intraaortic balloon pump and percutaneous





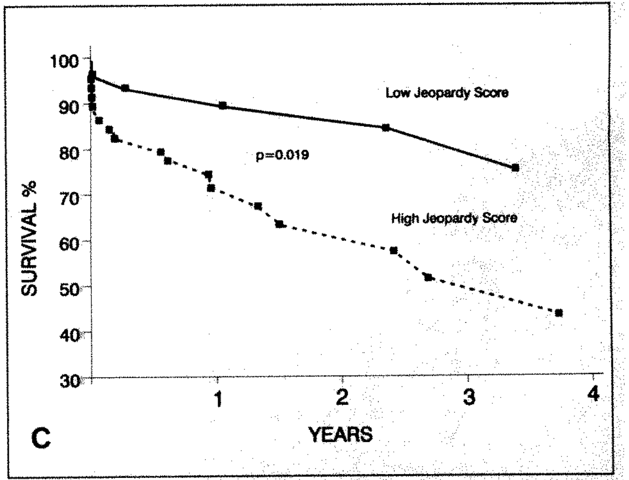


FIGURE 2. Survival curves in patients with favorable and unfavorable values for each independent variable are shown as *(A)* presence versus absence of congestive heart failure, *(B)* left ventricular ejection fraction (LVEF) >30 versus ≤30% and *(C)* high (>0.30) versus low (≤0.30) baseline jeopardy score for contractile myocardium.

cardiopulmonary bypass were used in only 15 and 5% of patients, respectively.

Several investigational methods have been proposed to protect LV regional function during balloon inflation.[19-23] However, no data are available on the routine use of these methods during PTCA in patients with severe LV dysfunction.

Increased mortality during follow-up after percutaneous transluminal coronary angioplasty in patients with left ventricular dysfunction and determinants of survival: In the study of Dorros et al,[7] 22 late deaths (22%) occurred in a mean of 3.2 years after PTCA. Similarly, Kohli et al[8] reported a 24% mortality during 12 to 45 months (average 22) of follow-up. In our study, the 4-year estimated survival was 57 ± 8%. In this group of high-risk patients, identification of features associated with increased mortality is critical for patient selection and treatment. Clinically, the survival after PTCA was most adversely affected by the presence of congestive heart failure and very low LV ejection fraction. This is further supported in published surgical reports indicating the increased operative mortality in patients with congestive heart failure.[24,25] The myocardial jeopardy score for contractile segments before PTCA was an angiographic indicator of the amount of potentially ischemic myocardium and was an independent predictor of mortality in our study. Jeopardy score for contractile myocardium was a better predictor of survival than global jeopardy score, emphasizing the importance of the amount of myocardium at risk for future events. The extent of coronary disease was a strong risk factor for hospital mortality among 8,207 PTCA procedures analyzed by Ellis et al.[26]

With the available data, it is difficult to determine the impact of restenosis on survival. As in previous reports,[27,28] incomplete revascularization itself was not associated with increased risk of mortality once the effects of baseline variables are taken into consideration.

Comparison with surgical revascularization: Because there are no randomized data available, it is difficult to compare the results of PTCA in patients with LV dysfunction with a natural history of CAD or with the results of coronary artery bypass surgery. Operative mortality at coronary bypass surgery increases with the severity of LV dysfunction and may be as high as 7% in patients with very poor LV performance (LV ejection fraction <19%) according to the Coronary Artery Surgery Study.[5] However, a more significant survival benefit after coronary artery bypass surgery over medical treatment is apparent in patients with LV dysfunction, despite an increased operative mortality.[2-4] In studies comparing surgical and medical treatment in patients with LV dysfunction, the survival benefit gained from coronary artery bypass surgery is usually not evident until several years after surgery.[2-4] Comparable long-term results for PTCA in this high-risk patient subgroup are not available. Data from our institution suggest that the LV function is a significant predictor of long-term survival after PTCA in patients with multivessel disease.[28]

Study limitations: Our study has several limitations inherent in this type of retrospective analysis. In a small proportion of patients undergoing PTCA, no left ventriculograms were available. Therefore, these patients were not included in the series. The cutoff point for ejection fraction of 40% was arbitrarily chosen to be comparable to previous reports. Left anterior oblique left ventriculograms provide additional information on LV function that may not be apparent on single-plane right anterior oblique angiograms. Data were accumulated over several years, during which performance of PTCA procedures underwent some changes (e.g., the use of percutaneous cardiopulmonary bypass).

Clinical implications: Our results showed that a high-risk subset can be identified among patients with severe LV dysfunction who undergo PTCA. Those with congestive heart failure or extensive CAD with large amounts of potentially ischemic myocardium and those with worse LV systolic function are at particularly high risk.

Acknowledgment: We thank the J.G. Mudd Cardiac Catheterization Team and Donna Sander for manuscript preparation.

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Effects of Diltiazem on Complications and Restenosis After Coronary Angioplasty

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A randomized, placebo-controlled, double-blinded trial was performed to evaluate the usefulness of empiric therapy with a calcium antagonist in patients who undergo coronary angioplasty. A total of 201 patients were randomized to placebo or to high-dose diltiazem (mean dose, 329 mg/day). Treatment began 24 hours before angioplasty. Restenosis was assessed by percent area stenosis as determined by quantitative angiographic techniques before, immediately and 1 year after angioplasty. All patients also received aspirin and dipyridamole before angioplasty. Heparin and verapamil were administered intravenously during the procedure. The 2 groups were similar with respect to age, extent of coronary artery disease, smoking history, and baseline lipid levels. Procedural complications, including death (1 vs 1), Q-wave infarction (0 vs 3), acute occlusion (5 vs 5) and focal spasm (0 vs 0), were not significantly different in the diltiazem and placebo patients, respectively. Freedom from all acute complications was noted in 85% of patients in both groups. One-year angiographic follow-up was obtained in 60% of patients. Restenosis rates were similar: 36% in the diltiazem group and 32% in the placebo group (p = 0.30). The incidence of late cardiac events (death, Q-wave myocardial infarction, recurrent angina or coronary bypass graft surgery) was similar in the 2 groups. Thus, diltiazem did not influence the overall restenosis rate or prevent late events after coronary angioplasty.

(Am J Cardiol 1991;67:373–376)

Calcium antagonists are theoretically attractive agents for use after coronary angioplasty. By reducing smooth muscle contraction at the angioplasty site, calcium antagonists might minimize ongoing endothelial trauma and platelet deposition in the early hours after the procedure. Vasospasm at the site of angioplasty during follow-up,[1] and elastic recoil[2,3] of the dilated segment, have also been implicated as causes of chronic restenosis. Calcium antagonists have been shown to retard the development of atherosclerosis in animal models,[4-8] and preliminary evidence suggests that this class of drugs may inhibit the development of new atherosclerotic lesions in humans as well.[9,10] Diltiazem and verapamil have mild antiplatelet activity,[11-13] and all calcium antagonists have been shown to provide cardioprotection during and after ischemia.[14-16] Thus, although there are many potential reasons for the empiric use of calcium antagonists in patients undergoing coronary angioplasty, clinical data on the actual conferred benefits are less well documented.[17] The purpose of the current study was to evaluate the usefulness of diltiazem in preventing acute complications, restenosis and recurrent cardiac events after elective coronary angioplasty.

METHODS

A total of 201 patients were enrolled in this randomized, placebo-controlled, double-blinded trial evaluating oral diltiazem for the prevention of restenosis after coronary angioplasty. Patients were excluded from study participation for angioplasty performed for an evolving acute myocardial infarction, high-grade atrioventricular block, sick-sinus syndrome, recent thrombolytic administration, or other severe concomitant medical illnesses. Both diltiazem and placebo were given on a 3 times per day dosing schedule. The diltiazem dose ranged from 240 to 360 mg per day (mean, 329 mg). Treatment began 24 hours before angioplasty. All patients received at least 1 dose before the procedure. Compliance monitoring revealed that 96% of all dispensed pills were ingested.

Angioplasty protocol: Elective coronary angioplasty was performed using our standard protocol.[18] In this regimen, patients are pretreated for at least 24 hours with 325 mg of aspirin daily and dipyridamole 75 mg 3 times a day. The patients were routinely pretreated with 5 mg of intravenous verapamil, 75 mg of intravenous lidocaine, 5 mg of sublingual isosorbide dinitrate, 50 mg of dextran, and 10,000 units of intravenous heparin. A repeat heparin bolus of 5,000 units was given intrave-

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From Cardiovascular Consultants, Inc., Mid America Heart Institute, St. Luke's Hospital, Kansas City, Missouri. This study was supported in part by a research grant from Marion Merrell Dow Laboratories, Kansas City, Missouri. Manuscript received August 6, 1990; revised manuscript received and accepted October 10, 1990.

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TABLE I Demographic Characteristics

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
Female/male (%)	14/88 (13.7/86.3)	18/81 (18.2/81.8)	0.44
Family history of heart disease (%)	54 (52.9)	52 (52.5)	1.00
Diabetes mellitus (%)	6 (5.9)	9 (9.1)	1.00
Cigarette smoking (%)	73 (71.6)	79 (79.8)	0.43
Total cholesterol >240 mg/dl (%)	13 (12.7)	15 (15.2)	0.19
Blood pressure >145/90 mm Hg (%)	42 (41.2)	35 (35.4)	0.69
Chronic lung disease (%)	4 (3.9)	3 (3.0)	1.00
Peripheral vascular disease (%)	3(2.9)	3 (3.0)	1.00

nously at hourly intervals during the procedure. Immediately after angioplasty, a continuous intravenous heparin infusion was initiated for approximately 24 hours. During follow-up, other cardiac medications were used as needed; calcium antagonists and β-blocking drugs were avoided. Patients were contacted by telephone or office visits, or both, at 2, 4, 6, 9 and 12 months after angioplasty.

Quantitative angiography: Coronary stenoses were measured by quantitative angiographic techniques. The quantitative measurement was based on computer-assisted vessel and lesion reconstruction in 2 orthogonal views (Figures 1 and 2). This technique corrects for x-ray beam divergence and pin-cushion distortion and allows for accurate, absolute stenosis measurements, as well as a percent area stenosis calculation. Restenosis was defined as return to ≥70% or luminal area stenosis and loss ≥50% of the initial gain with angioplasty. Percent area stenosis and absolute minimal luminal diameter were also evaluated as continuous variables. In this model, restenosis is defined as the change in the mean from immediately after angioplasty to follow-up.

RESULTS

Randomization resulted in 102 patients in the diltiazem and 99 patients in the placebo groups. The 2 groups were similar with respect to demographic and baseline angiographic characteristics (Table I). In-hospital complications were similar in the 2 groups (Table II). Acute reocclusion occurred in 5% of both groups. An insignificant trend toward a lower incidence of procedure-related Q-wave myocardial infarction was noted in the diltiazem group.

Complete angiographic follow-up was available in 120 patients (60%). A single lesion was dilated in 63 patients, and 57 patients underwent multilesion percutaneous transluminal coronary angioplasty. Quantitative analysis showed a decrease in the mean area stenosis from 85% before percutaneous transluminal coronary angioplasty to 50% immediately after, and to 63% at the time of the follow-up angiogram. These changes were similar in the 2 groups (Figure 3). The changes in minimal absolute luminal diameter also were not different in the 2 groups (Figure 4). The overall patient restenosis rate was 36% in the diltiazem and 32% in the placebo groups (p = 0.30). Late cardiac events, including recurrent angina, death, Q-wave myocardial infarction and need for elective coronary artery bypass graft surgery during follow-up, occurred with similar frequency in the 2 groups (Table III). Laboratory values at baseline and at 1-year follow-up were similar in the 2 groups (Table IV). Recurrent angina pectoris during follow-up occurred in 46 and 37% of diltiazem- and placebo-treated patients, respectively.

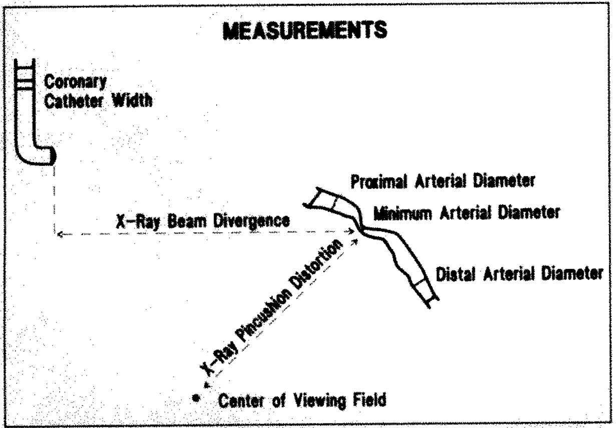

FIGURE 1. Quantitative angiographic technique uses measurements of the minimal proximal and distal arterial diameters. Catheter is used as the reference standard, allowing for accurate, absolute measurements. Corrections are made for x-ray beam divergence and pincushion distortion.

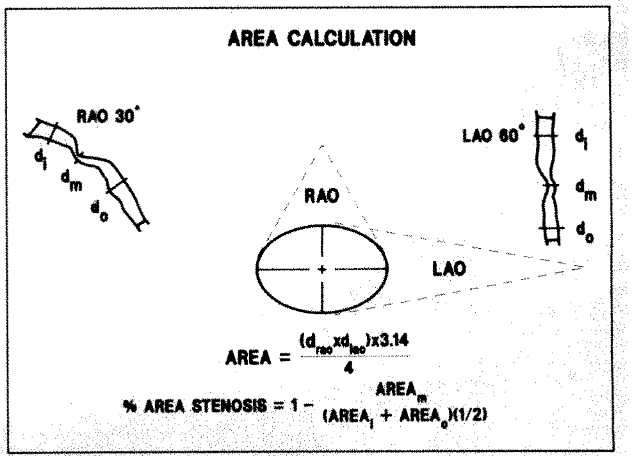
AREA CALCULATION
RAO 30°
d_i
d_m
d_o
RAO
LAO 60°
d_i
d_m
d_o
LAO
$\text{AREA} = \frac{(d_{rao} x d_{lao}) x 3.14}{4}$
$\% \text{ AREA STENOSIS} = 1 - \frac{\text{AREA}_m}{(\text{AREA}_i + \text{AREA}_o)(1/2)}$

FIGURE 2. Area calculations are based on diameter measurements made in 2 orthogonal views. di = inlet diameter; dm = minimal diameter; do = outlet diameter; LAO = left anterior oblique; RAO = right anterior oblique.

TABLE II Percutaneous Transluminal Coronary Angioplasty Complications

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
None (%)	87 (84.5)	83 (84.5)	NS
Death (%)	1 (0.9)	1 (1.0)	NS
Q-wave AMI (%)	0	3 (3.1)	0.12
Acute occlusion (%)	5 (4.9)	5 (5.1)	NS
Emergency surgery (%)	3 (2.9)	2 (2.0)	NS
Dysrhythmia (%)	0	1 (1.0)	NS
Unstable angina (%)	1 (0.9)	2 (2.0)	NS
Intimal dissection (%)	4 (3.8)	4 (4.1)	NS
Ventricular fibrillation (%)	0	0	NS
Shock (%)	2 (1.9)	0	NS
Focal spasm	0	0	NS

AMI = acute myocardial infarction; NS = difference not significant.

TABLE III Events During Follow-Up

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
Death (%)	3 (3)	0	0.24
CABG (%)	1 (1)	1 (1)	1.00
Q-wave MI (%)	0	1 (1)	0.49
Angina (%)	38 (37)	39 (39)	0.46

CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

TABLE IV One-Year Laboratory Values

	Treatment		
	Diltiazem	Placebo	p Value
Total cholesterol (mg/dl)	172 ± 96	188 ± 93	0.3
HDL cholesterol (mg/dl)	24 ± 17	25 ± 15	0.7
Triglycerides (mg/dl)	125 ± 103	138 ± 100	0.4
Creatine kinase	88 ± 86	84 ± 91	0.8
Albumin (g/dl)	3 ± 2	4 ± 2	0.5
BUN/creatinine ratio	10 ± 6	10 ± 8	0.8
Total protein (g/dl)	5 ± 3	6 ± 3	0.4
Albumin/globulin ratio	1 ± 1	1 ± 1	0.6

BUN = blood urea nitrogen; HDL = high-density lipoprotein.

DISCUSSION

Aspirin and calcium antagonists have been used empirically after coronary angioplasty since Gruentzig et al[19] first introduced the procedure 13 years ago. Aspirin has stood the test of time and, although it does not prevent restenosis, it has proven highly effective in preventing acute vessel closure after coronary angioplasty.[20,21] Convincing clinical evidence to support the routine use of calcium antagonists after elective angioplasty does not exist. The results of the current study suggest that diltiazem does not prevent restenosis or recurrent cardiac events after coronary angioplasty.

Acute vessel closure: Abrupt, acute or subacute vessel reocclusion after coronary angioplasty is generally the result of intimal and medial disruption with flap formation, thrombus accumulation and coronary vasospasm. The problem of coronary vasospasm after angioplasty is probably underappreciated by many clinicians. A study using quantitative stenosis measurements with sequential angiograms in the first several hours after dilation demonstrated routine progressive coronary vasoconstriction in the dilated segment.[22] This vasospasm occurs even in patients pretreated with aspirin and calcium antagonists, which suggests that it results from a direct receptor-mediated or myogenic response to arterial injury. This reflex vasoconstriction can be reversed or prevented by nitroglycerin. Although diltiazem was ineffective in preventing acute vessel reocclusion in this series, all patients were routinely pretreated with sublingual isosorbide dinitrate and intravenous verapamil. Additionally, transcutaneous nitroglycerin was used for the first 24 to 48 hours after angioplasty. It is possible that diltiazem may be useful in preventing acute events due to abrupt vessel closure as a consequence of coronary vasospasm in patients who are not pretreated with nitrates or verapamil, although this question was not addressed in the current study.

Restenosis: Restenosis is emerging as a major focus of cardiovascular research efforts. This is a complex pathophysiologic process that involves more than one

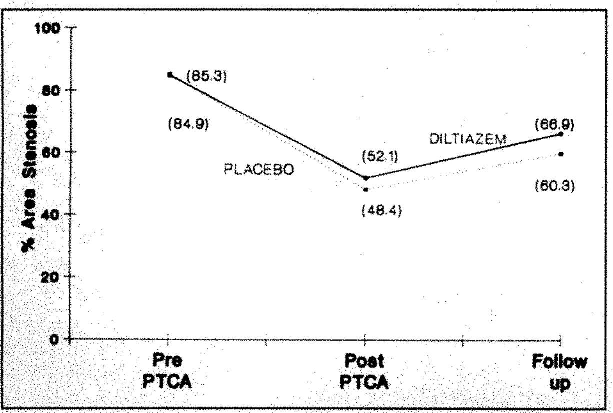

FIGURE 3. Changes in the mean area percent stenosis in the diltiazem *(solid line)* and placebo *(dotted line)* groups were similar during the study (difference not significant). PTCA = percutaneous transluminal coronary angioplasty.

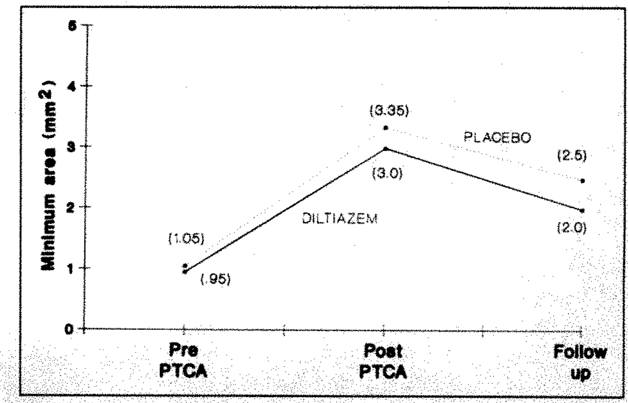

FIGURE 4. Changes in the minimal absolute area stenosis were similar in the 2 groups during the study. PTCA = percutaneous transluminal coronary angioplasty.

mechanism. Myointimal smooth muscle cell proliferation is the most common histologic picture,[23,24] although elastic recoil of the vessel wall has also been implicated as a cause of late luminal narrowing after coronary angioplasty.[2,3] It is theorized that this elastic recoil is independent of medial injury (unlike the proliferative response) and involves overstretching of the vessel. Restenosis in this scenario is the result of gradual "restitution of tone" of the overstretched segment. The results of this study, as well as previous reports,[25,26] suggest that calcium antagonists are ineffective in preventing this type of restenosis. Abnormal vasomotion in the dilated coronary segments has been observed to occur frequently for up to 6 months after angioplasty. One study documented an abnormal response to ergonovine provocation in 28% of patients.[27] Although the restenosis rate was high (50%) in patients with provocable coronary spasm, pretreatment with high-dose nifedipine did not prevent the abnormal vasomotor response.

Thus, calcium antagonists, like all pharmacologic and nonpharmacologic approaches used to date, appear ineffective in reducing the restenosis rate after coronary angioplasty in humans.

Recurrent cardiac events: Perhaps the most surprising result of this trial was the ineffectiveness of diltiazem in preventing recurrent angina or cardiac events during follow-up. No differences were noted with respect to the incidence of recurrent angina pectoris, acute myocardial infarction, coronary bypass graft surgery, or death during follow-up between patients treated with diltiazem or placebo. Diltiazem and other calcium antagonists, as well as β blockers and nitrates, can mask the clinical recurrence of angina pectoris in patients with restenosis. It is uncertain why this effect was not observed in the present trial, although it may in part relate to the use of concurrent antianginal medications in the study patients.

On the basis of previously reported trials, most cardiologists have come to the realization that calcium antagonists probably do not importantly influence the occurrence of restenosis after coronary angioplasty. However, many centers continue to use calcium antagonists routinely after angioplasty to prevent subacute and chronic events.[17] The results of this study suggest that calcium antagonists need not be routinely used unless a distinct indication (angina, hypertension, incomplete revascularization, and so forth) is present.

Study limitations: Although this was a randomized, double-blinded, placebo-controlled study using quantitative angiography, the angiographic follow-up rate was relatively low at 60%. The sample size (patient number) was too small to detect a modest ($\leq$25%) reduction in the restenosis rate, although the analysis of restenosis as a continuous variable using quantitative angiographic definitions increases the power of the study.[28] The routine use of nitrates and verapamil during the procedure probably obscured to some degree the effect of diltiazem on acute events early after angioplasty.

Acknowledgment: We thank Joel Greenberg, MD, and Jeffrey Osborne, MD, for their efforts on this project.

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Atrial Natriuretic Peptide Response to Cardioversion of Atrial Flutter and Fibrillation and Role of Associated Heart Failure

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and Suman Vardan, MD

Plasma atrial natriuretic peptide (ANP) concentrations were measured before and 1 hour after cardioversion in 40 patients (27 with atrial flutter and 13 with atrial fibrillation) admitted for elective cardioversion. Fourteen (11 with atrial flutter and 3 with atrial fibrillation) had clinical evidence of congestive heart failure (CHF). Conversion to sinus rhythm was successful in 39 patients. The mean ANP concentration in the entire group decreased after cardioversion from 38 ± 4 to 17 ± 2 pmol/liter ($p < 0.001$). In the subgroup with CHF, the ANP level, which was not significantly higher than that in the group without CHF, decreased from 47 ± 8 to 19 ± 3 pmol/liter ($p < 0.01$). Neither mode of cardioversion (spontaneous 1, pharmacologic 2 and direct-current countershock 36) nor associated CHF influenced ANP response to cardioversion. One patient with atrial flutter and "failed cardioversion" had unchanged ANP level. The decrease after cardioversion in ANP concentration correlated with its control level ($r = 0.88$, $p < 0.001$) but not with the decrease in heart rate. The ANP level in patients with atrial fibrillation was 45 ± 9 vs 38 ± 5 pmol/liter in those with atrial flutter (difference not significant). Arrhythmia duration, left atrial size, and ventricular rate or arterial blood pressure did not correlate with ANP concentration in any subgroup. It is concluded that (1) the ANP level is elevated comparably in patients with both atrial flutter and fibrillation regardless of the presence or absence of CHF; and (2) the level decreases, independent of the mode of cardioversion or presence of CHF, promptly after successful cardioversion.

(Am J Cardiol 1991;67:377–380)

Atrial natriuretic peptide (ANP) is released from atrial myocytes not only in congestive heart failure (CHF), but also in atrial and ventricular tachyarrhythmias.[1–4] A ventricular origin of ANP in severe ventricular dysfunction reported recently is less in amount than that from the atria.[5,6] However, the mechanism of ANP release from the atria still remains controversial, particularly in the setting of cardiac arrhythmias. For example, in atrial arrhythmias, whether the fast atrial rate itself or the associated elevation of atrial pressure, or both, contribute to this increase continues to be a subject of debate.[7,8] Repetitive electrical stimulation of the isolated left atrium has been observed to release ANP in the perfusate bathing the atrial preparation, indicating that stimulation frequency was the modulator of ANP release in this setting.[7] Electrical cardioversion of spontaneous or induced supraventricular arrhythmias reduces elevated plasma ANP levels along with a concomitant decrease in atrial pressure.[9] The purpose of our present noninvasive clinical study was to investigate in humans the ANP profile in sustained atrial flutter and fibrillation and the ANP response to cardioversion. We wished to determine if the atrial rate, which is obviously faster and very irregular in atrial fibrillation, generated higher plasma ANP levels than it did in atrial flutter, and if any associated CHF contributed to elevation of ANP concentration in these settings. In addition, we explored the role of the mode of cardioversion (spontaneous, pharmacologic or electrical) and the use of the anesthetic agent on the ANP response to conversion of the arrhythmia to sinus rhythm. In patients who had CHF associated with atrial arrhythmia, we examined whether persistence of CHF after cardioversion influenced the plasma ANP levels.

METHODS

Patients: We studied consecutively 38 men and 2 women, aged 52 to 86 years (mean ± standard error of the mean 68 ± 1), hospitalized for elective cardioversion. Twenty-seven of them had atrial flutter (age 68 ± 1 years) and 13 had atrial fibrillation (age 68 ± 2 years).

The duration of atrial flutter ranged from 7 days to 12 months and that of atrial fibrillation from 3 hours (catheter-induced in a patient with coronary artery disease) to 4 months before cardioversion. Fourteen of 27 patients with atrial flutter had documented chronic obstructive pulmonary disease and the remaining patients

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had various other conditions such as coronary artery disease with or without hypertension, mitral valve disease, repair of atrial septal defect (1 patient) and excision of left atrial myxoma (1 patient). Seven of 11 patients with atrial fibrillation had angiographically documented coronary artery disease, 2 had dilated cardiomyopathy and the remaining 2 patients were, respectively, 2 weeks and 4 months status post aortic valve replacement.

During history taking special attention was paid to the duration of the atrial arrhythmia, associated etiologic factor or factors and presence or absence of indexes of CHF. The patients were carefully examined for evidence of elevated jugular venous pressure, S_3 gallop or basilar pulmonary rales. At least 2 of these 3 findings were required for a patient to be included in the CHF group. No patient needed right-sided cardiac catheterization for documentation or management of CHF in this study. In addition, routine electrocardiograms and echocardiograms were recorded, with the left atrial size measured from M-mode echocardiograms. All patients had been receiving digitalis therapy, while 14 of them were taking quinidine and 26 procainamide. The latter 2 drugs were added 24 hours before electrical cardioversion. On the morning of the day of cardioversion, performed in the medical intensive care unit, breakfast was omitted, digoxin was withheld and serum electrolyte levels determined. Electrical cardioversion was then attempted in 37 of 40 patients. The other 3 had reverted to sinus rhythm, 1 spontaneously (i.e., within 10 minutes of administration of quinidine gluconate orally) and 2 pharmacologically, after the administration of 3 or 4 doses of the antiarrhythmic agent. Under intravenous methohexital anesthesia, electrical cardioversion was performed using direct-current countershock 25 to 200 W seconds in patients with atrial flutter and 50 to 300 W seconds in those with atrial fibrillation. Before and 1 hour after cardioversion 10 ml of peripheral venous blood was drawn in ethylenediamine tetraacetate tubes on ice for determination of ANP concentration by a radioimmunoassay technique.[9] The sensitivity of the method in our laboratory has been 3 pg/ml and inter- and intraassay coefficients of variation were 18 and 12%, respectively. The patients were observed for 2 hours after cardioversion in the medical intensive care unit where vital signs, indexes of CHF and evidence for recurrence of arrhythmias were monitored. They were then transferred back to the floor care.

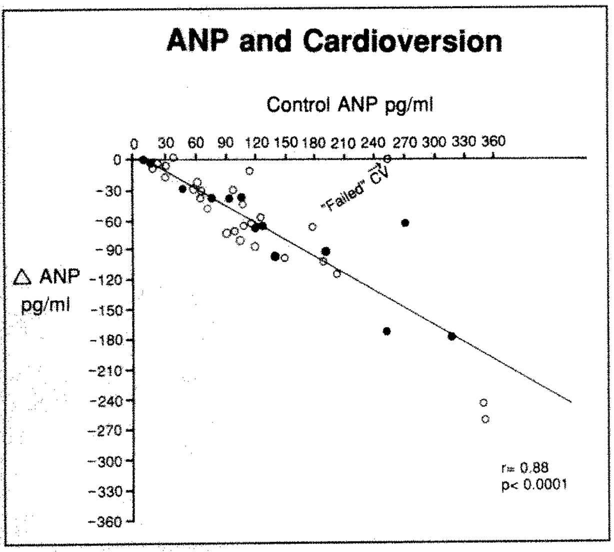

FIGURE 1. Relation between control plasma atrial natriuretic peptide (ANP) levels and their change after cardioversion. *Open circles* represent patients with atrial flutter; *closed circles* represent those with atrial fibrillation. The patient in whom cardioversion was unsuccessful ("failed" CV) had an unchanged elevated plasma ANP level. A significant correlation is evident between control plasma ANP levels and their decrease after cardioversion.

Statistical analysis of the data was performed using Student's *t* test for paired values, each patient acting as his own control, and values expressed as mean ± standard error of the mean.

RESULTS

Atrial arrhythmias and left atrial size: The left atrial size could be measured in 25 patients with atrial flutter and 10 with atrial fibrillation. In 5 patients the study was technically limited precluding accurate measurement. The mean left atrial size in the group with atrial flutter was 4.3 ± 0.2 cm (range 3.2 to 6.4) and that in the group with atrial fibrillation 4.2 ± 0.3 cm (range 2.5 to 5.7). The difference between the 2 groups was not significant.

Cardioversion, mode and outcome: Three patients did not need electrical cardioversion (see before), and of the remaining 37 requiring electrical cardioversion, 36 had conversion to sinus rhythm (24 had atrial flutter and 12 had atrial fibrillation). The single patient with "failed" cardioversion had atrial flutter for 3 days complicating a massive inferior and right ventricular infarction.

Atrial natriuretic peptide levels, duration of arrhythmia, heart rate, blood pressure, left atrial size and cardioversion: Except in the patient in whom cardioversion was unsuccessful (see before) and in whom ANP concentration was unchanged, 83 pmol/liter (250 pg/ml), the plasma ANP level decreased in the entire group of patients with atrial arrhythmia from a mean of 38 ± 4 to 17 ± 2 pmol/liter (115 ± 13 to 51 ± 7 pg/ml) ($p < 0.001$). It decreased in the group with atrial flutter from 38 ± 5 to 16 ± 2 pmol/liter (114 ± 16 to 49 ± 73 pg/ml) ($p < 0.01$), and in the group with atrial fibrillation from 45 ± 9 to 21 ± 5 pmol/liter (134 ± 27 to 62 ± 16 pg/ml) ($p < 0.05$). The difference in ANP levels between the 2 groups was not statistically significant. The duration of the arrhythmia did not correlate with plasma ANP concentration in either subgroup. Regardless of the arrhythmia subset, the control level of the ANP correlated strongly with its decrease after cardioversion ($r = 0.88$, $p < 0.001$, Figure 1). With regard to heart rate (control mean heart rate in the entire group was 100 ± 4 beats/min and decreased after cardioversion to 75 ± 2 beats/min, $p < 0.001$), the ventricular rate did not correlate with the plasma ANP levels.

The mean systolic and diastolic blood pressures in the group with atrial flutter before cardioversion were 128 ± 4 and 81 ± 2 mm Hg, respectively. After cardioversion the values were 128 ± 4 and 77 ± 3 mm Hg (difference not significant [NS]). In the group with atrial fibrillation the control mean systolic and diastolic blood pressures were, respectively, 140 ± 6 and 87 ± 3 mm Hg and after cardioversion were 148 ± 6 and 84 ± 3 mm Hg (NS). The control mean blood pressure for the entire group was 103 ± 9 mm Hg and after cardioversion 97 ± 2 mm Hg (NS). Neither systolic, diastolic nor the mean blood pressure in either group correlated with plasma ANP levels either during atrial arrhythmia before or in sinus rhythm after cardioversion. The left atrial size also did not correlate with ANP level in either subgroup.

Atrial natriuretic peptide levels, heart failure and response to cardioversion (Figures 2 and 3): Eleven patients with atrial flutter and 3 with atrial fibrillation had clinical indexes of CHF before and after cardioversion (successful in 13 and unsuccessful in 1 patient). The control plasma ANP levels in 13 patients with successful cardioversion was 41 ± 8 pmol/liter (142 ± 25 pg/ml), and decreased to 19 ± 3 pmol/liter (58 ± 9 pg/ml) after cardioversion (p <0.01). The plasma ANP levels in the 26 patients without CHF (16 with atrial flutter and 10 with atrial fibrillation) decreased from 33 ± 5 pmol/liter (100 ± 14 pg/ml) to 16 ± 3 pmol/liter (48 ± 9 pg/ml) (p <0.01).

DISCUSSION

An increase in plasma ANP concentration in atrial arrhythmias has been attributed to associated elevation of atrial pressure in these circumstances.[3,4,7] Likewise, the decrease after cardioversion in ANP concentration

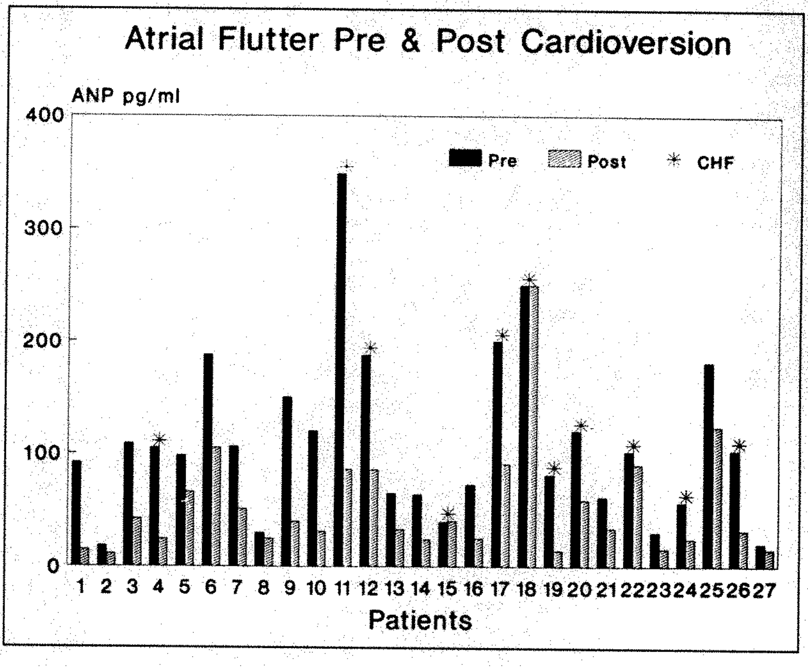

FIGURE 2. Plasma atrial natriuretic peptide (ANP) levels before and after cardioversion in individual patients with atrial flutter. Cardioversion lowered the plasma ANP levels in most patients with atrial flutter including those with persistent congestive heart failure (CHF). In patient 18 cardioversion was unsuccessful. Except for patient 11 with CHF who had the highest plasma ANP concentration, many other patients with CHF (nos. 4, 15, 19, 20, 22, 24 and 26) did not have plasma ANP levels higher than those without CHF (nos. 3, 6, 9 and 25). Pre = before cardioversion; Post = after cardioversion; * patients with congestive heart failure.

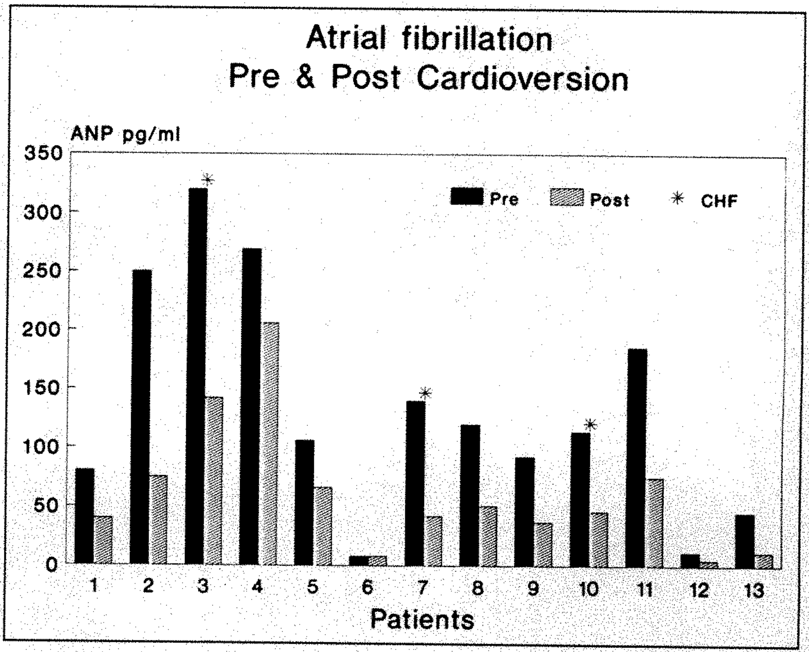

FIGURE 3. Plasma atrial natriuretic peptide (ANP) levels before and after cardioversion in individual patients with atrial fibrillation. The ANP levels decreased after cardioversion in all patients with high levels including those who had persistent congestive heart failure (CHF). Although the highest plasma ANP concentration was observed in a patient with CHF (no. 3), other patients with CHF (nos. 7 and 10) did not have higher ANP levels than in many patients without CHF (nos. 2, 4 and 11). Other abbreviations as in Figure 2.

has been explained by the decrease in atrial pressure resulting from restoration of sinus rhythm.[10] Although we did not assess atrial pressures quantitatively, our noninvasive data strongly suggest that atrial arrhythmia alone can cause elevation in plasma ANP concentration unrelated to changes in atrial pressure or their size in this setting.

In all 13 patients with CHF the indexes of CHF persisted after successful cardioversion, but their elevated plasma ANP levels decreased significantly by restoration of sinus rhythm (Figures 2 and 3).

Shiebinger and Linden[7] concluded from an electrical pacing study of isolated rat atrium on ANP release that the frequency of atrial contraction directly influenced the secretion of immunoreactive ANP from the atria. This suggests a similar role for atrial arrhythmias on ANP release in humans. Our arrhythmia patients with obvious CHF did not have significantly higher ANP levels than those without CHF. The mode of cardioversion, spontaneous, pharmacologic or electrical, also did not influence its effect on plasma ANP levels. Furthermore, the use of intravenous anesthesia did not alter the plasma ANP concentration. It was abolition of the atrial tachyarrhythmia and restoration of sinus rhythm that decreased the plasma ANP concentration unrelated to the mode of cardioversion or the presence of CHF.

With regard to atrial rate effects on ANP release, one can postulate that high frequency of atrial contractions in atrial flutter and its twitches in atrial fibrillation cause increased release of ANP from the atrial cardiocytes elevating plasma levels of this hormone. These elevated levels fall promptly with the restoration of sinus rhythm and a slower atrial rate. Although the atrial rate is obviously higher in atrial fibrillation than that in atrial flutter, the plasma ANP levels did not differ significantly between the 2 groups. Whether the frequent and irregular atrial twitches in atrial fibrillation are not sufficiently organized to induce greater ANP release from the myocytes than that caused by less frequent but more organized atrial activity in atrial flutter remains speculative.

Thus, our present data indicate that (1) the high plasma ANP levels in atrial flutter and fibrillation are unrelated to left atrial size, arrhythmia duration, ventricular rate or blood pressure; (2) presence of CHF does not seem to contribute to high ANP levels in this setting; (3) plasma ANP levels do not differ significantly between patients with atrial flutter and those with atrial fibrillation; and (4) the ANP levels fall promptly and consistently after cardioversion regardless of the use of anesthesia or the mode of cardioversion.

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Sudden Cardiac Death While Wearing a Holter Monitor

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The Holter tapes of 61 patients (46 men, mean age ± standard deviation 65 ± 11 years) with sudden cardiac death while being monitored were analyzed. Thirty-eight patients were known to have coronary artery disease, 5 had cardiomyopathy, and 7 had aortic valve disease. Etiology remained unknown in 11 patients. Mean New York Heart Association functional class was 2.5 ± 0.7. Thirty patients had received antiarrhythmic drugs and 32 had received digitalis. Sudden death occurred at rest in 73%. In the hours before death, repetitive ventricular arrhythmias were found in 50 patients (82%), with atrial fibrillation in 34%. Patients with bradyarrhythmic death (18%) had less complex ventricular activity compared to patients with tachyarrhythmic death ($p < 0.01$). Lethal arrhythmias—monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, torsades de pointes, primary ventricular fibrillation, and 1:1 conducting atrial tachycardia—were found in 26 (43%), 15 (25%), 5 (8%), 3 (5%), and 1 patient, respectively. The coupling interval of the final ventricular tachycardia correlated inversely with the initial frequency of ventricular tachycardia ($p < 0.05$). For patients with tachyarrhythmic death, an increase of heart rate within the last 3 hours was noted (83 vs 89 beats/min, $p < 0.05$). Ventricular premature complexes and the proportion of patients with >2 couplets and >2 triplets increased significantly only within the last hour before death. The R-on-T phenomenon was observed in 12 patients (20%), 10 of whom died from tachyarrhythmia. In 6 cases, the arrhythmia was initiated by the R-on-T phenomenon ($p < 0.01$). Thus, monomorphic ventricular tachycardia was the arrhythmia most frequently associated with sudden cardiac death. Increase in heart rate before death was small and clinically insignificant. Increase in complex ectopy was noted only within the last hour. Patients with monomorphic ventricular tachycardia lasting longer than polymorphic tachycardia or torsades de pointes (165 vs 24 or 19 seconds, respectively) have the best chance of successful resuscitation.

(Am J Cardiol 1991;67:381–386)

The terminal electrical events leading to sudden cardiac death are rarely recorded on Holter monitor. Recently, several reports appeared on series, generally small, of patients who died while wearing a Holter monitor. However, whether sudden death in these patients is preceded by typical "warning" arrhythmias that might identify a patient as being in imminent danger remains unclear. Whereas some studies claim that sudden death is preceded by warning arrhythmias,[1–4] others strictly deny this.[5,6] To settle this issue, the recordings of 61 patients with sudden death were analyzed.

METHODS

Patient group: Seventy-two tapes with recordings of sudden death were collected from 1985 to 1988. However, not all of them fulfilled the criteria for inclusion in the study. Sudden cardiac death was defined as natural, unexpected death due to cardiac causes within 1 hour of the onset of acute symptoms, with or without preexisting cardiac disease.[7] Patients with New York Heart Association class IV heart failure, with evident pulmonary embolism, cardiac tamponade or heart failure after accident were not included in the study, nor were patients with unstable angina or myocardial infarction within the last 3 weeks. Two tapes with insufficient recording quality (i.e., >20% artifacts) were rejected.

Ambulatory electrocardiographic analysis: The final 61 tapes were analyzed by means of the Reynolds Pathfinder® III system. First, a complete—if possible—2-channel documentation at a speed of 3 to 5 mm/s was printed. Lethal and any questionable arrhythmias were printed at a speed of 25 mm/s. The complete printout was visually analyzed 3 times for rate, rhythm, frequency, complexity and duration of ventricular ectopic activity (ventricular premature complexes, pairs, nonsustained ventricular tachycardia [3 to 5 beats, >5 beats but <30 seconds] and sustained ventricular tachycardia [>30 seconds]). The type of final tachycardia (mono-, polymorphic, torsades de pointes) was classified.[8] Its duration was measured from the initiating ectopic beat to the moment of degenerating into ventricular fibrillation characterized by grossly irregular rhythm with

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TABLE I Clinical Characteristics

Pt. Group	Pt. No./ Male	Age (yr)	Cardiac Diseases CAD/CMP/AVD	History of Syncope +/0	NYHA Class	SCD at Rest +/0	Digitalis Medication (%)	Antiarrhythmics (%)	Death (%)
All pts.	61/46	65 ± 11	38/5/7	15/20	2.5 ± 0.7	30/11	70	64	77
Bradyarrhythmia	11/9	71 ± 9	7/0/1	3/1	2.3 ± 0.8	6/0	33	100	100
Tachyarrhythmia*	50/37	64 ± 12	31/5/6	12/19	2.6 ± 0.7	24/11	75	61	74
Mono. VT	26/20	64 ± 11	18/3/2	7/9	2.7 ± 0.7	13/5	76	59	67
Poly. VT	15/13	64 ± 13	9/2/2	3/9	2.3 ± 0.6	7/4	69	62	80
Torsades	5/3	61 ± 12	1/0/2	1/1	2.5 ± 0.6	3/1	100	67	67
Primary VF	3/1	77 ± 16	3/0/0	1/0	3.0 ± 0.0	1/1	67	67	100
Unknown data (n)	—	—	11	26	21	20	15	14	13

* One patient with 1:1 conducting atrial flutter is not listed separately.
Percentages are related to the number of patients whose characteristics were known.
Values are mean ± standard deviation.
AVD = aortic valve disease; CAD = coronary artery disease; CMP = cardiomyopathy; Mono. = monomorphic; NYHA = New York Heart Association; Poly. = polymorphic; SCD = sudden cardiac death; torsades = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

baseline undulations and a frequency >400 per minute. Primary ventricular fibrillation was defined as ventricular fibrillation without previous bradyarrhythmia or ventricular tachycardia[7] (Figure 1). Bradyarrhythmic arrest was assumed in the absence of normal function of sinus node or atrioventricular junction, or both, and failure of normal subordinate activity to assume pacemaking function.[7] In an extra run, ST-segment changes >0.2 mV and lasting >2 minutes and R-on-T phenomena were identified visually. All lethal arrhythmias were analyzed separately by 2 of the authors. If mutual agreement could not be reached, a third cardiologist was consulted.

Analysis of data: Clinical data on invasive and noninvasive procedures, occupation at the time of death, medication and autopsy were incomplete in some patients. Thus, percentages are related to the number of patients whose characteristics were complete (Table I).

The time before death was analyzed in 1-hour intervals. The last hour was divided into six 10-minute intervals. Because of unequal numbers of monitored hours, the corresponding hours before death were superimposed and the data averaged. Thus, from the 24th hour to the last hour, an increasing number of patients were included in the analysis (e.g., ≥ 42 patients in the last 6 hours).

Data are given as mean ± standard deviation or median for nonparametric distribution. Normally distributed data were compared by means of Student's *t* test, and abnormally distributed data by means of the U test. Comparison of ≥ 2 incidences was made by multifield chi-square analysis. With 2-tailed testing, statistical significance was established at a p value <0.05.[9]

RESULTS

Clinical findings: The study comprised 61 patients (46 men, mean age ± standard deviation 65 ± 11 years). Of these, 11 patients (18%) died from bradyarrhythmia and 50 patients (82%) from tachyarrhythmia (Table I). Patients with bradyarrhythmic death were older than patients with tachyarrhythmic death (71 vs 64 years, $p < 0.01$). In 11 patients, exact cardiac diagnosis remained unknown. At least 38 patients had coronary artery disease, 4 had dilated and 1 hypertrophic cardiomyopathy, 7 had aortic valve disease (2 had pure stenosis, 1 a prosthetic valve, 3 had stenosis and regurgitation, 1 had pure regurgitation). A history of syncope was found more often in bradyarrhythmic than in tachyarrhythmic patients (75 vs 39%, $p < 0.05$). Mean functional class was 2.5 ± 0.7 with no significant difference between the subgroups. Seventy-three percent of the patients with known history were sleeping or at rest when they died (Table I).

In 47 patients, drug history was available; however, among the bradyarrhythmic patients, 5 histories were incomplete. In the tachyarrhythmic group, 75% of pa-

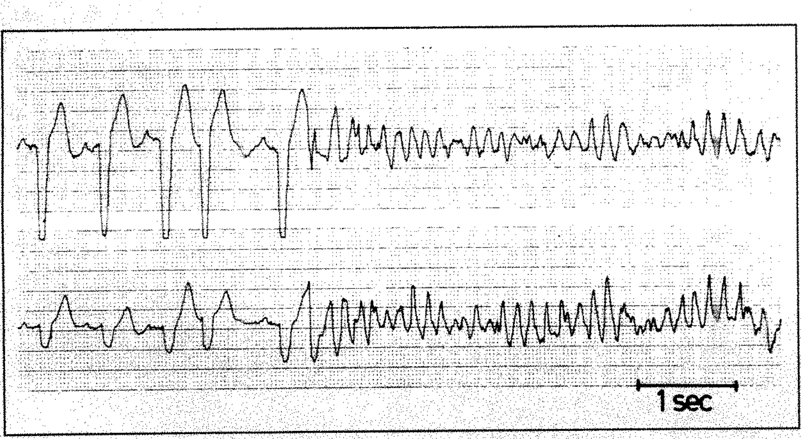

FIGURE 1. Primary ventricular fibrillation as lethal tachyarrhythmia. R-on-T ectopic beat resulting in grossly irregular rhythm. Frequency = 400 beats/min.

TABLE II Holter Data

Pt. Group	No. of Pts.	Rhythm SR/AF	BBB	VPB Only	Triplets/ nVT	Heart Rate 4th hour/10′	ST Elevation	Final QTc	Initial R-on-T	Initial Rate of VT/min	Duration of VT (Median, seconds)
All pts.	61	40/21	16	11	34	—	10	—	13	—	—
Bradyarrythmia	11	6/5	2	5	3	86/79	4	444 ± 80	—	—	—
Tachyarrhythmia*	50	34/16	14	6	31	83/89	6	437 ± 80	13	246 ± 66	85
Mono. VT	26	15/11	9	3	16	85/93	3	437 ± 58	6	226 ± 57	165
Poly. VT	15	14/1	2	3	8	86/84	2	431 ± 65	4	268 ± 70	24
Torsades	5	3/2	2	0	4	66/70	0	482 ± 88	0	248 ± 68	19
Primary VF	3	2/1	1	0	2	74/95	1	416 ± 85	3	—	—

* One patient with 1:1 conducting atrial flutter is not separately listed.
Values are mean ± standard deviation.
AF = atrial fibrillation; BBB = bundle branch block; nVT = nonsustained ventricular tachycardia; SR = sinus rhythm; VPB = ventricular premature beats; other abbreviations as in Table I.

tients had received digitalis, with no difference between the subgroups. At least 30 patients were receiving antiarrhythmic therapy (20 were receiving class I, 4 class II, 4 class III and 6 class IV antiarrhythmic drugs). Four were receiving 2 different agents. It is noteworthy that ≥55% of the bradyarrhythmic deaths may have been related to antiarrhythmic therapy: 2 patients were receiving β blockers, 2 patients class III agents, and 2 patients calcium antagonists. All bradyarrhythmic patients died; 26% of the tachyarrhythmic patients could be resuscitated (Table I).

Rhythm: Permanent or intermittent atrial fibrillation was found in 21 patients (34%), with no significant difference between the brady- and tachyarrhythmic patients (45 vs 32%, difference not significant; Table II). Intermittent atrial fibrillation became permanent at the end of recording in 86% of these patients.

Bradycardiac arrest: Bradyarrhythmic arrest was complete atrioventricular block with slow fascicular or idioventricular rhythm in 4 patients and sudden asystole arrest in 7 patients. Four of 11 patients (36%) compared to 6 of 50 patients (12%) in the tachyarrhythmic group exhibited significant ST elevation in the minutes before death ($p < 0.05$). Bradyarrhythmic patients had less repetitive ventricular ectopic activity compared to tachyarrhythmic patients ($p < 0.01$; Table II). Likewise, the median of ventricular premature beats was lower than that of tachyarrhythmic patients. Within the last hour, heart rate decreased from 97 to 77 beats/min ($p < 0.01$; Figure 2).

Tachyarrhythmic arrest: As the final tachyarrhythmia, monomorphic ventricular tachycardia was found in 26 (43%), polymorphic tachycardia in 15 (25%), torsades de pointes in 5 (8%), primary ventricular fibrillation in 3 patients (5%) and atrial flutter with a frequency of 170 beats/min in 1 patient (Tables I and II). All patients with cardiomyopathy and 6 patients with aortic valve disease died a tachyarrhythmic death. Increased ectopic activity was found in tachyarrhythmic patients: 31 patients (62%) exhibited triplets and nonsustained ventricular tachycardia in the hours before death, compared to 27% of bradyarrhythmic patients ($p < 0.01$). Only 6 patients had no repetitive ventricular ectopic activity in the hours before death.

Ventricular arrhythmias: The median of ventricular premature beats did not change within the last 6 hours before death, except for the last hour: During this hour, the median increased from 60 to 196 beats per hour (Figure 2), and the proportion of patients with >500

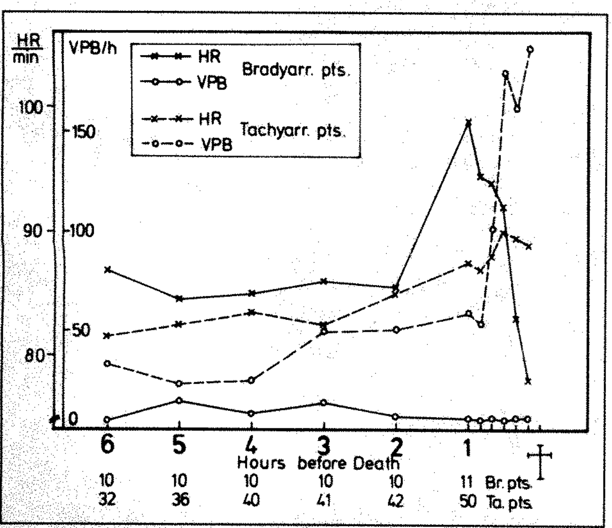

FIGURE 2. Mean heart rate (HR) and median of ventricular premature beats (VPB) during the last 6 hours before death. The numbers of included bradyarrhythmic (Br. pts.) and tachyarrhythmic (Ta. pts.) patients are given below the corresponding hour.

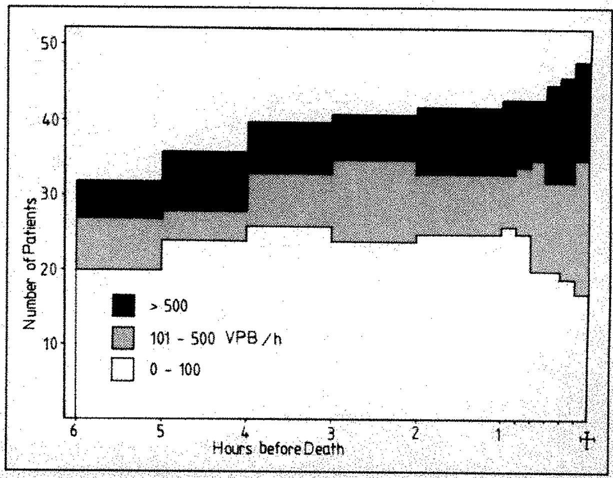

FIGURE 3. Hourly frequency of ventricular premature beats (VPB) in tachyarrhythmic patients during the last 6 hours before death.

ventricular premature beats per hour reached 14% (Figure 3). The same was found for repetitive ectopic ventricular activity: Whereas during the first 4 hours (6 to 2) before death the proportion of patients with a higher incidence of couplets and triplets (nonsustained ventricular tachycardia) remained constant, the proportion of patients with ≥3 triplets per hour increased up to 42% during the last hour ($p < 0.05$; Figures 4 and 5).

To establish more specific criteria with which to identify patients prone to tachyarrhythmic death, the recordings were analyzed for each of the following criteria: (1) occurrence of >3 triplets (nonsustained tachycardia) in any 1 hour before death; (2) occurrence of >6 triplets (nonsustained tachycardia) in any 1 hour; (3) occurrence of at least 1 episode of nonsustained ventricular tachycardia with >10 consecutive ectopic beats. Using these criteria, (1) 40%, (2) 26% and (3) 18% of all patients could be identified in the hours before death in only 1 bradyarrhythmic patient. Also, using these criteria, 30, 20 and 12% of the patients could have been identified within the last 10 minutes.

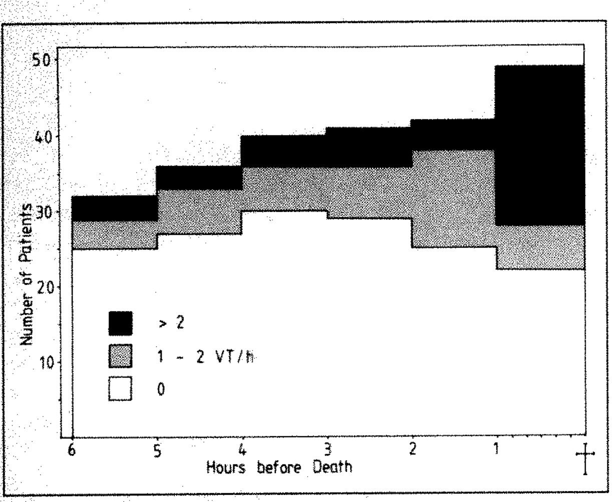

FIGURE 4. Hourly frequency of couplets in tachyarrhythmic patients during the last 6 hours before death.

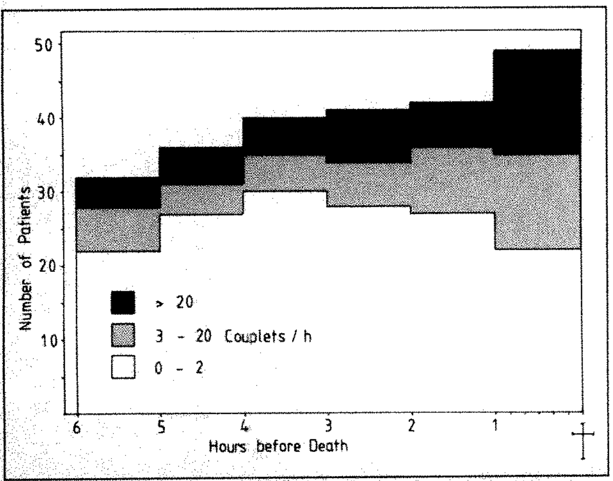

FIGURE 5. Hourly frequency of ventricular runs in tachyarrhythmic patients during the last 6 hours before death. VT = ventricular tachycardia ≥3 QRS <30 seconds.

Heart rate: An increase in heart rate within the last 3 hours was noted (83 vs 89 beats/min, $p < 0.05$; Figure 2). This increase could not be demonstrated in all tachyarrhythmic subgroups: Patients with polymorphic tachycardias or torsades de pointes showed no significant change in heart rate. Only 6 tachyarrhythmic patients exhibited significant ST-segment changes. The rate-corrected QT duration before death was increased only in patients with torsades de pointes (Table II).

Ventricular tachycardia: The mean initial rate of ventricular tachycardia was 246 ± 66 beats/min, with the highest rate of 268 ± 70 beats/min among patients with polymorphic tachycardia (difference not significant). Patients with monomorphic tachycardia had the longest duration of degenerating into ventricular fibrillation compared to patients with polymorphic ventricular tachycardia and patients with torsades de pointes (median 165 vs 24 and 19 seconds, respectively; Table II). Because minimal cardiac output is maintained during ventricular tachycardia, patients with long-lasting tachycardia had the best chances of successful resuscitation. Thus, in 14 patients with monomorphic tachycardia, resuscitation was successful in 50%, whereas it was successful in only 30% of patients with polymorphic tachycardia.

Coupling interval and R-on-T phenomena: In the hours before death, the R-on-T phenomenon was observed in 12 patients (20%), 10 of whom died from tachyarrhythmia. In 13 patients (26% of the tachyarrhythmic patients), the lethal tachyarrhythmia was initiated by an R-on-T ectopic beat (Table II). Six of these had already exhibited R-on-T ectopic beats in the hours before death. Thus, the proportion of patients with R-on-T phenomenon before death was higher among patients whose final arrhythmia was initiated by R-on-T than among patients whose final arrhythmia had a longer coupling interval ($p < 0.05$).

Figure 6 shows the inverse correlation between the final coupling interval and the initial rate of tachycardia

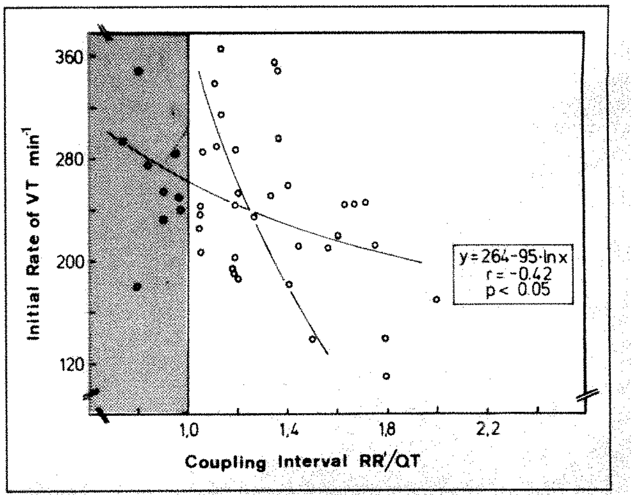

FIGURE 6. Inverse relation between final coupling interval and initial frequency of ventricular tachycardia in 44 patients. VT = final ventricular tachycardia.

in 44 patients ($p < 0.05$). Of the remaining 6 patients, 3 died from primary ventricular fibrillation. In 3 patients, the coupling interval could not be exactly determined because of artifacts.

DISCUSSION

This second largest series of patients with sudden death during Holter monitoring—the largest series, of 69 patients, was compiled by Leclercq et al[10]—demonstrates that monomorphic ventricular tachycardia is the arrhythmia most frequently associated with sudden cardiac death (43%; Leclercq et al, 32%). It persists longer than polymorphic ventricular tachycardia (25%; Leclercq et al, 16%) or torsades de pointes (8%; Leclercq et al, 17%) before degenerating into ventricular fibrillation, thus resulting in a better chance of resuscitation. Bradyarrhythmic death (18%; Leclercq et al, 22%) was found in older patients and is associated with a worse prognosis. Antiarrhythmic (64%) and digitalis therapy (75%) were similarly distributed among all tachyarrhythmic subgroups and comparable to Leclercq et al's study (antiarrhythmics, 57%). However, all 6 bradyarrhythmic patients whose drug histories were known had been treated for tachyarrhythmias, compared to only 62% of tachyarrhythmic patients who received antiarrhythmic drugs (Table I). Whether these bradyarrhythmic patients died because of antiarrhythmic treatment remains unclear.

Heart rate: Heart rate remained unchanged until the last premortal hour, and mean increase was <10 beats/min within the last hour. In light of the physiologic variance of heart rate, this change is too small for clinical decision-making. In bradyarrhythmic patients, change in heart rate was more pronounced and may therefore be of greater clinical relevance: Within the last hour, mean decrease was >20 beats/min. Leclercq et al[10] found a comparable increase of heart rate, from 83 to 90 beats/min, in tachyarrhythmic patients within the last hour. However, Kempf et al[1] stated that there was a ≥20% increase in heart rate in 11 of 20 tachyarrhythmic patients within the last hour. Other authors reporting smaller series could not demonstrate a premortal change in heart rate.[2–6]

"Warning arrhythmias": A significant increase in ventricular ectopic activity (premature beats, >2 couplets/hour, >2 triplets/hour) could only be demonstrated in tachyarrhythmic patients during the last hour. The clinical value of this observation remains questionable: A 100 to 200% increase of repetitive ectopic activity could be mimicked by spontaneous variability.[11] The documented arrhythmia profile is also found in patients with dilated cardiomyopathy who are not candidates for imminent sudden death.[12] Missing repetitive ventricular activity does not exclude sudden death: 6 patients in the tachyarrhythmic group (12%) showed no premortal repetitive ventricular ectopy. Criteria such as 6 triplets per hour (nonsustained tachycardia) in any hour, or a ventricular tachycardia, or both, with >10 consecutive ectopic beats, are more specific, but less sensitive. With these 2 criteria, only 25% of all patients could be identified in the present study. Thus, this study confirms the findings of previous investigators[1–4] that ventricular ectopic activity increases toward arrhythmic death. However, the instantaneous prognostic value of this increase is limited.

ST changes and R-on-T phenomena: Premortal ST-segment changes >0.2 mV and lasting >2 minutes could be identified clearly in 10 patients (16%), with a higher incidence in patients with bradyarrhythmic death (Table II). However, Holter monitoring has certain limitations in recording ST-segment changes.[13] Thus, it must be anticipated that the incidence of ischemia as a trigger of lethal arrhythmias is probably higher than found in this study. In a recent review, ST changes were reported in 12 to 26% of all patients; however, ST changes were not mentioned in several of the reports.[14] The importance of the R-on-T phenomenon is still debatable: Whereas some authors[2,6,15] found a high incidence of initiating R-on-T ectopic beats, others deny any prognostic relevance of the R-on-T phenomenon.[1,5] One problem of the R-on-T ectopic beat is the analysis of tapes: It must be performed visually; this was not done in most studies. The present, visually controlled study confirmed that a final tachycardia is more likely to be initiated by an R-on-T ectopic beat, if this ectopic beat is also found in the hours before death.

Other studies: Until now, about 250 cases of sudden cardiac death during Holter monitoring have been reported. Numerous studies of 6 to 15 patients have been published,[2–6,14,15] but only 2 studies included a relatively larger series, of 27 and 69 patients, respectively.[1,10] In a recent survey, Bayes de Luna et al[14] reviewed the reports of 157 patients, whose data are in good agreement with those of the present study. Reliable conclusions can only be drawn from samples of reasonable size. The main reason for the many conflicting results in the different studies is the small number of patients. The question of warning arrhythmias, however, is not answered in detail by Kempf,[1] Leclercq,[10] and their co-workers, because their patients' data were not superimposed continuously.

Study limitations: The patients in this series, who had histories of syncope and received digitalis, diuretic and antiarrhythmic drugs, comprise a highly select group. Because of arrhythmic problems, their physicians ordered Holter recordings. Thus, the present data cannot be transferred to patients without cardiac disease or to those with cardiac disease who are not wearing Holter recorders when they die.

Acknowledgment: We thank all of our colleagues who helped us conduct this study and supplied us with the tapes and histories of their patients: D. Andresen, MD, R. Henzgen, MD, K. Schüren, MD, and N. Wrobel, MD, Berlin; G. Argenton, MD, Gross-Gerau; O. Baldus, MD, D. Steffel, MD, and F. Webering, MD, Cologne; D. Barth, MD, Neumünster; H. Becker, MD, Hanau; B. Burg, MD, Simmern; A. Feige, MD, Hamburg; F. de Haan, MD, Solingen; P. Heimburg, MD, Stuttgart; E. Hoberg, MD, and G. Schuler, MD, Hei-

delberg; B. Klein, MD, Kaufungen; E. Köhler, MD, E. Meyn, MD, and D. Schaf, MD, Bad Salzuflen; D. Koronczewski, MD, Lauffen; K. Kothmann, MD, and D. Seibold, MD, Bayreuth; J. Kraatz, MD, and P. Nissen, MD, Mannheim; L. Krehan, MD, Darmstadt; E. Lutz, MD, Mainz; H. Ohlmeier, MD, Bad Oeynhausen; H. Petri, MD, and G. Schmidt, MD, Munich; C. Piper, MD, and D. Rouhi, MD, Wiesbaden; J. Senges, MD, Ludwigshafen; D. Röhl, MD, Bad Soden; D. Rönsberg, MD, Bergisch-Gladbach; D. Rouhi, MD, Wiesbaden; E. Schmidt, MD, Bernried; D. Storp, MD, Laatzen; G. Weber, MD, Backnang; H. Weber, MD, Vienna; and W. Zoll, MD, Erftstadt-Frauenthal.

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Late Results of the Left Subcostal Approach for Automatic Implantable Cardioverter Defibrillator Implantation

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A left subcostal surgical approach was used to implant an automatic implantable cardioverter defibrillator (AICD) in 48 patients with a history of nonfatal cardiac arrest or documented ventricular tachycardia/fibrillation. Electrophysiologic studies before surgery yielded induction of monomorphic or polymorphic ventricular tachycardia in 40 patients, whereas 8 were noninducible. Mean (± standard deviation) age was 58 ± 12 years. Mean ejection fraction was 33 ± 16%. Thirty patients (63%) had documented coronary artery disease; 14 patients (29%) had previous coronary bypass surgery. The mean intraoperative defibrillation threshold was 13.8 ± 6.6 J. In 6 patients, an adjunctive right minithoracotomy was used to position 1 patch over the right atrium and thus optimize the defibrillation threshold. Patients with prior exposure to amiodarone and previous coronary bypass surgery had higher defibrillation thresholds at implantation. Two perioperative deaths occurred. There were no infections. Long-term follow-up yielded a 1- and 5-year survival of 0.88 and 0.58, respectively, and a freedom from sudden cardiac death of 1.0 and 0.97, respectively. The nonthoracotomy, left subcostal surgical approach is safe and effective, provides adequate defibrillation thresholds in most patients, and yields long-term survival comparable to other implantation techniques.

(Am J Cardiol 1991;67:387–390)

The efficacy of the automatic implantable cardioverter defibrillator (AICD) for the management of malignant ventricular tachyarrhythmias is now well established.[1] A number of surgical approaches have been described for the implantation of the lead system: median sternotomy,[2] left thoracotomy,[3] subxiphoid,[4] left subcostal[5] and subcutaneously.[6] We use the left subcostal approach exclusively, unless contraindicated, as in the presence of intraabdominal infection. Also, when concomitant coronary artery bypass or valve surgery is planned, a median sternotomy is used. This report describes clinical results in 48 consecutive patients undergoing implantation of the AICD via the left subcostal approach who were followed for up to 6 years.

METHODS

Patients: All patients had a history of nonfatal cardiac arrest or ventricular tachycardia/fibrillation not related to acute myocardial infarction. Patients not inducible in the electrophysiology laboratory or inducible but refractory to multiple drug trials were evaluated for AICD implantation. To evaluate late outcome, only patients followed for a minimum of 1 year or until death are reported here.

Baseline electrophysiologic studies were performed without sedation and at ≥5 half-lives after administration of antiarrhythmic drugs. Serial studies were performed in patients with inducible ventricular tachycardia in order to evaluate the efficacy of antiarrhythmic drugs.

Intraoperative defibrillation threshold assessment: Alternating current was used to induce ventricular fibrillation. The pulse generator (External Cardioverter Defibrillator, Cardiac Pacemakers, Inc. [CPI], St. Paul, Minnesota) used for defibrillation testing delivered a single monophasic truncated exponential wave form pulse. Defibrillation threshold, defined as the least energy that would defibrillate the heart 15 seconds after induction of ventricular fibrillation on ≥2 separate occasions, was determined as follows: the initial defibrillation pulse of 15 J was administered 15 seconds after induction of ventricular fibrillation. If cardioversion to sinus rhythm was not achieved, defibrillation was again attempted with 20 J. If persistently unsuccessful, the pulse amplitude was increased to 25 J and a third defibrillation pulse delivered. If ventricular fibrillation persisted, subsequent shocks of 30 and 40 J were delivered before an external 200 J rescue shock was used.

From the Cardiac Electrophysiology Unit, Departments of Medicine (Division of Cardiology) and Surgery, Baylor College of Medicine and The Methodist Hospital, Houston, Texas. Computational assistance was provided by the CLINFO project, funded by the Division of Research Resources of the National Institutes of Health under RR-00350. Manuscript received June 11, 1990; revised manuscript received October 2, 1990, and accepted October 5.

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Polarity was then reversed to determine which patch polarity configuration produced the lowest defibrillation threshold. Ventricular fibrillation was reinduced and the process repeated, beginning with 15 J. If successful defibrillation was noted at any level (<20 J) in either polarity, we first confirmed the effectiveness of this level with another induction. If the initial 15-J pulse was successful, defibrillation efficacy was also assessed at progressively lower energy settings (10, 5, 3, 2 J). If defibrillation was unsuccessful at any test, the patient was defibrillated using the preceding energy setting. Polarity was reversed and, after induction of ventricular fibrillation, defibrillation was attempted using the last successful energy setting (that is, the defibrillation threshold established with the previous polarity). If successful, progressively smaller energy settings were used in the new configuration. Reproducibility of defibrillation was confirmed at the lowest energy setting that successfully terminated ventricular fibrillation. A minimal rest period of 4 minutes was taken between successive inductions of ventricular fibrillation.

Hardware: Before the CPI Ventak series 1500 became available, 2 patients received the prototype automatic implantable defibrillator (AID). Subsequent patients received CPI Ventak models 1500, 1510, 1520 and, more recently, the programmable 1550. The all-epicardial patch configuration with 2 large defibrillation patches (CPI model L67) was used exclusively. Two epicardial screw-in leads were used for bipolar sensing.

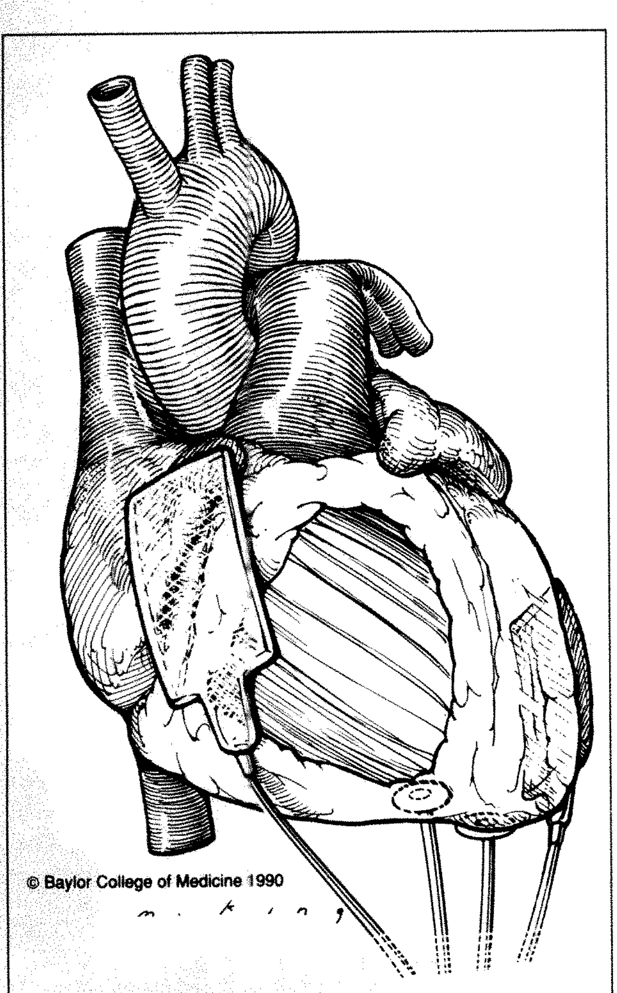
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FIGURE 1. Artist's impression of patch electrode placement on the surface of the heart. Note the anterior patch encompasses much of the right ventricular outflow tract.

Surgical technique: The technique of left subcostal thoracotomy for implantation of the AICD has been described previously.[5] The subcostal approach alone was used in 42 patients. In 6 patients who had undergone previous cardiac surgery and who had unacceptable transventricular defibrillation thresholds (>20 J), a right minithoracotomy (an anterior incision made at the level of the right atrium through the bed of the fourth or fifth costal cartilage) was added to the left subcostal approach to access the right atrium for patch placement in an intrapleural extrapericardial position.[7] In the first 35 patients, both large defibrillation patches were placed on the left ventricle as the initial patch configuration. The final configuration was decided on the basis of intraoperative testing with different patch positions and polarities. In 6 of the 35 patients, unacceptable defibrillation thresholds (>20 J) led to the placement of 1 patch against the right atrium through a right minithoracotomy. The observed improvement in defibrillation threshold in these 6 patients[7] led to the routine of placing 1 patch as far to the right as possible to include the diaphragmatic surface of the right ventricle and part of the right atrium as the initial configuration in the last 13 patients (Figure 1).

One patch was placed intrapericardially on the diaphragmatic surface of the ventricles. The other was placed extrapericardially in patients who had undergone previous cardiac surgery and intrapericardially in the remainder. The 2 screw-in sensing leads were placed inferiorly on the right ventricular apex, with an interelectrode distance of 1 cm. All defibrillator generators were placed posterior to the rectus muscle through the same subcostal incision.

Postoperative care: After completion of the surgical procedure, the AICD was activated. All patients were transferred to the intensive care unit from the operating room. After 24 hours of observation they were transferred to the floor, unless hemodynamic or ventilatory parameters precluded this.

Statistical analysis: Data are presented as mean ± standard deviation. The paired *t* test was used for intragroup comparisons; the unpaired *t* test was used for intergroup comparisons. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics: The mean (± standard deviation) age of the 48 patients (32 men, 16 women) was 58 ± 12 years (range 28 to 75). The ejection fraction ranged from 12 to 80% (mean 33 ± 16%). Twenty-two patients presented clinically with nonfatal cardiac arrest, and 26 patients had ventricular tachycardia with associated syncope. Coronary artery disease was documented in 30 patients, whereas 18 patients had nonischemic cardiomyopathy. At preoperative electrophysiologic testing, monomorphic ventricular tachycardia was induced in 7 patients, polymorphic ventricular tachycardia in 3 patients and ventricular fibrillation in 30 patients. Eight patients remained noninducible after up to 4 extra stimuli, 4 drive cycle lengths and 2 right ventricular sites were used. Left ventricular stimulation was not attempted. Preoperatively inducible patients underwent a mean of 3 (range 0 to 7) antiarrhythmic drug trials.

Operative data: Satisfactory defibrillation thresholds were obtained in 6 patients with initial thresholds >30 J only after a right minithoracotomy had been performed in order to position 1 patch against the right atrium.[7] This procedure reduced defibrillation thresholds to a mean of 20.8 ± 3.8 J ($p < 0.05$). The mean defibrillation threshold in the overall patient population was 13.8 ± 6.6 J.

Patients who had received amiodarone before surgery (n = 20) had significantly higher thresholds than those who did not (16.0 ± 6.0 vs 12.2 ± 6.6, $p < 0.05$) (Figure 2). Patients who had previous coronary artery bypass surgery (n = 14) also had higher thresholds than those who had not (18.6 ± 6.0 vs 11.8 ± 5.8, $p < 0.01$) (Figure 3). Two patients died perioperatively: 1 from an acute myocardial infarction 2 days after surgery and another from incessant ventricular tachycardia that led to cardiogenic shock on the day after surgery. The AICD was not activated in the latter patient. One patient developed a postoperative pericardial tamponade, which was explored and evacuated without deleterious sequelae. There were no postoperative infections.

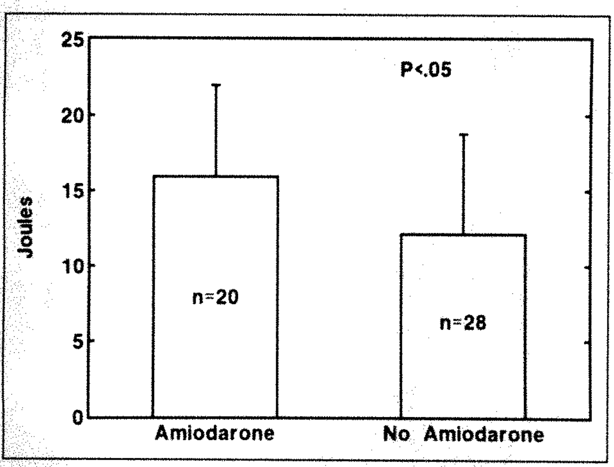

FIGURE 2. Effect on defibrillation threshold of prior exposure to amiodarone.

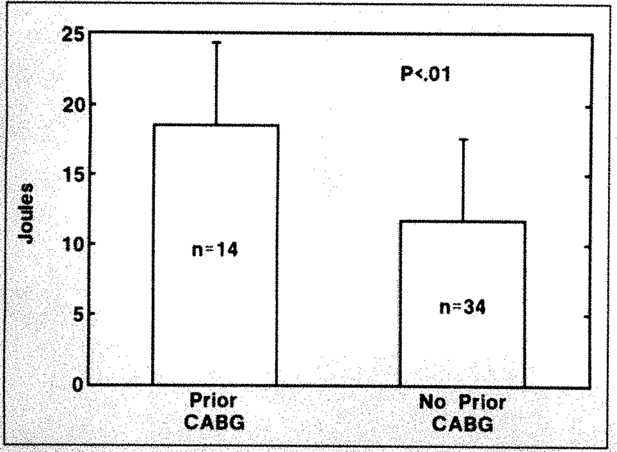

FIGURE 3. Effect on defibrillation threshold of previous coronary artery bypass surgery. CABG = coronary artery bypass graft.

Follow-up: The patients were followed for a mean of 27 ± 16 months (range 0 to 69). No atrial dysrhythmias occurred intraoperatively or were documented during subsequent follow-up. Fourteen patients had 15 generator replacements at an average of 21 ± 8 months. Survival analysis by the Kaplan-Meier method revealed an overall patient survival at 1 year of 0.88 and at 5 years of 0.58. However, freedom from arrhythmic death was 1.0 at 1 year and 0.97 at 5 years (Figure 4). Of the 11 late deaths in this series, 5 were from progressive heart failure, 2 were from cerebrovascular accidents, 1 was from leukemia and 1 followed heart transplantation and rejection. Two deaths were sudden and presumed arrhythmic. In 1 of these patients, the device sensed appropriately and delivered serial shocks but presumably failed to convert the rhythm. The other patient's device was explanted 3 years before his death. He refused reimplantation. From the point of view of survival analysis, data in relation to this patient were censored at the time of explantation. Defibrillators discharged appropriately in 25 patients at a mean of 14 ± 20 times (range 1 to 93). One patient died from progressive heart failure 3 months after surgery. With the exception of this patient and the 2 perioperative deaths, all patients survived a minimum of 1 year.

DISCUSSION

We have shown the safety and efficacy of the left subcostal surgical approach in 48 patients undergoing AICD implantation for nonfatal cardiac arrest or ventricular tachycardia refractory to drug therapy. The operation was performed with minimal morbidity and mortality attributable to the technique. In addition, postoperative convalescence was rapid, generally allowing discharge from the intensive care setting within 24 hours. However, in 6 patients, manipulation of patch positions through the subcostal incision failed to produce a satisfactory defibrillation threshold. All 6 had had previous cardiac surgery. We performed a right minithoracotomy in them to allow placement of 1 patch

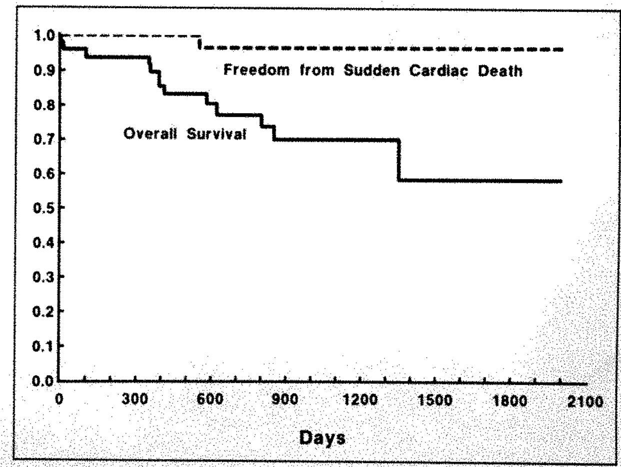

FIGURE 4. Kaplan-Meier survival curves for overall survival and freedom from sudden cardiac death.

against the right atrium and thereby reduced the defibrillation threshold to acceptable levels. Placement of 1 patch over the right atrium has not resulted in an increased incidence of atrial tachyarrhythmias.

The left subcostal approach was initially described for epicardial pacemaker implantation.[8] With the development of the AICD, we have successfully modified the approach for the implantation of its lead and generator systems.[5] The present study extends our previous observations and confirms the feasibility of the subcostal surgical approach in the majority of patients undergoing AICD implantation.

There have been conflicting reports on the influence of preoperative amiodarone on intraoperative thresholds.[9,10] We observed in the present study that patients on amiodarone have in general had higher defibrillation thresholds than the rest of the patient population. Patients who had previous cardiac surgery also had higher defibrillation thresholds.

Long-term follow-up reveals satisfactory device function. Chronic defibrillation thresholds determined at the time of generator replacement were ≤20 J in the patients undergoing replacement. Overall survival and long-term freedom from arrhythmic death was similar to that reported using alternative surgical techniques.

Acknowledgment: We gratefully acknowledge the secretarial assistance of Nigar Rasheed in the preparation of this manuscript.

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Influence of Dilated Cardiomyopathy, Myocarditis and Cardiac Transplantation on the Relation Between Plasma Atrial Natriuretic Factor and Atrial Pressures

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To determine whether dilated cardiomyopathy, myocarditis or cardiac transplantation affect the relation between plasma immunoreactive atrial natriuretic factor (ANF) and cardiac filling pressures, right atrial plasma ANF concentration, pulmonary arterial wedge pressure and right atrial pressure were measured in patients with dilated cardiomyopathy (n = 48), dilated cardiomyopathy secondary to myocarditis (n = 20) and prior cardiac transplantation (n = 34). ANF level significantly correlated with both pulmonary arterial wedge and right atrial pressures in patients with dilated cardiomyopathy; however, the presence or absence of myocarditis did not significantly alter these relations (p = 0.88 and p = 0.33 for interaction terms, respectively). For the combined group the ANF–pulmonary arterial wedge pressure relation had a slope of 8.1 pg/ml/mm Hg (95% confidence interval (CI), 5.4 to 10.8; p = 0.0001) and the ANF–right atrial pressure relation a slope of 13.6 pg/ml/mm Hg (CI, 8.5 to 18.7; p = 0.0001). Receiver operator curve analysis identified an optimal dividing point of ANF 150 pg/ml with 100% (CI, 72 to 100%) of patients with right atrial pressure ≥8 mm Hg having ANF ≥150 pg/ml, but only 56% (CI, 42 to 69%) with pressure <8 mm Hg having ANF <150 pg/ml. Unlike the patients with cardiomyopathy (with or without myocarditis), cardiac transplant recipients displayed no correlation between ANF level and either pulmonary arterial wedge pressure (p = 0.50) or right atrial pressure (p = 0.29) despite similarly elevated ANF concentrations (mean ± standard deviation, 168 (83) pg/ml in transplant patients versus 185 (114) pg/ml in cardiomyopathy patients). It is concluded that left and right intracardiac pressures are important determinants of circulating ANF level unaffected by inflammation in patients with cardiomyopathy. Factors other than filling pressures influence circulating ANF in a significant number of patients with cardiomyopathy and in all transplant recipients.

(Am J Cardiol 1991;67:391–397)

Atrial natriuretic factor (ANF) is a peptide hormone[1] with natriuretic, diuretic and vasodilatory properties,[2-4] synthesized principally by atrial myocardium[2] and released in response to atrial distention.[5,6] Ventricular synthesis of ANF has been demonstrated in chronically failing hearts.[7-9] In patients with congestive heart failure, previous studies[10-15] have reported a linear relation between circulating ANF concentration and both right- and left-sided filling pressures.

Studies in murine[16,17] and human myocarditis[18] have suggested that myocardial inflammation can stimulate ANF synthesis. Whether this production occurs independently of loading conditions or alters circulating ANF level has not been determined. In addition to myocarditis, the effect of inflammation due to cardiac transplant graft rejection on ANF–filling pressure relations has not been studied. In fact, whether transplantation itself alters this relation remains controversial, since limited human studies have reported a correlation between filling pressures and ANF concentration[19,20]; however, animal models of denervation have found it to be abolished.[21,22]

We wished to identify influences of myocardial inflammation or cardiac transplantation on a linear ANF–filling pressure relation. In the present study, we measured right atrial plasma ANF level at the time of right heart hemodynamic assessment and endomyocardial biopsy in a large group (n = 102) of patients with dilated cardiomyopathy or postcardiac transplantation.

METHODS

Patients: The study group consisted of 82 of 94 consecutive patients presenting between July 1987 and June 1988 with congestive heart failure of ≤6 months' duration and 34 of 45 consecutive cardiac transplant patients presenting between November 1987 and June

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1988 for routine follow-up assessment of graft rejection. Twenty-three patients were not approached for entry into the study because of the unavailability of personnel. All patients were evaluated with a complete history and physical examination, echocardiography, right heart hemodynamic assessment and right ventricular endomyocardial biopsy, and entered the study after providing informed consent in accordance with institutional guidelines for human investigation. Right-sided cardiac catheterization was performed soon after presentation of patients whether or not symptomatic improvement had been maximized. All patients with cardiomyopathy were receiving diuretics and the majority angiotensin converting-enzyme inhibitors.

Echocardiography was used as a screen for dilated cardiomyopathy using end-diastolic dimension >6.0 cm and estimated ejection fraction <40% as entry criteria.[23,24] Eight of the 82 patients failed to meet this criteria and were excluded from analysis. The degree of systolic dysfunction was quantitated from the left ventricular stroke work and cardiac indexes determined at the time of right-sided cardiac catheterization. An additional 6 patients were excluded because of the presence of left ventricular aneurysm (n = 2), cardiac amyloidosis (n = 2), cardiac histiocytosis X (n = 1) or congenital heart disease (n = 1).

Right-sided cardiac catheterization and biopsy: Patients fasted overnight and underwent biopsy between 8 and 12 A.M. without premedication. A self-sealing percutaneous catheter sheath was placed into the internal jugular vein using 1% xylocaine for local anesthesia. A 10-ml sample of blood for ANF determination was drawn immediately through a triple-lumen catheter placed in the right atrium. Endomyocardial right ventricular biopsies were performed with standard technique using the Stanford-Caves bioptome. Pressure measurements were obtained with the triple lumen catheter in the right atrial, right ventricular, pulmonary arterial and pulmonary arterial wedge positions. Cardiac outputs were determined in triplicate using the thermodilution technique with <10% variability between measurements. Left ventricular stroke work index was calculated from the formula (cardiac index/heart rate) × (mean arterial pressure − pulmonary arterial end-diastolic pressure) × 13.6.

Histologic diagnosis: Four to 6 right ventricular biopsy specimens were obtained from each patient, sectioned into 2 to 4 pieces and fixed by immediate immersion in 10% formalin. Each specimen was paraffin-embedded, sectioned, stained with hematoxylin and eosin, and examined at a minimum of 4 levels. The following variables were quantitated: number of foci of myocyte necrosis; the amount, distribution and cellular composition of any inflammatory infiltrate; the extent and distribution (replacement or interstitial) of fibrosis; and the presence or absence of significant myocardial cell hypertrophy.[25]

Myocarditis was histologically diagnosed according to the Dallas criteria[26] by the presence of mononuclear infiltrates with myocyte necrosis. Borderline myocarditis biopsy samples demonstrated myocardial inflammation without myocyte necrosis. Biopsy specimens of patients with dilated cardiomyopathy (without myocarditis) had evidence of myocardial cell hypertrophy with varying degrees of interstitial fibrosis.[25] The degree of cardiac transplant rejection was determined from endomyocardial biopsy specimens using the Billingham criteria.[27] The influence of myocardial inflammation on the ANF–atrial pressure relations was assessed using the combined group of patients with myocarditis and borderline myocarditis and then by excluding the patients with borderline myocarditis.

Plasma atrial natriuretic factor radioimmunoassay: Blood samples were collected in tubes containing 1.5 mg/ml ethylene diaminetetraacetic acid and 20 μg of aprotinin (Sigma Chemical Co., St. Louis, Missouri) and promptly centrifuged (2,000 g for 15 minutes). Plasma was separated, immediately frozen and stored at −70°C. ANF was extracted from plasma samples using preactivated C18 octadecyl silica cartridges (Sep Pak C18, Waters Associates, Milford, Massachusetts), reconstituted and processed in duplicate with a human ANF radioimmunoassay kit (Peninsula Laboratories, Bemont, California), which used a polyclonal rabbit antisera raised against human α ANF (1–28). The intra- and interassay coefficients of variation were 10 and 27%, respectively, and the assay detection limit was 4 pg/tube.[28]

Statistical methods: Linear regression coefficients and 95% confidence intervals were calculated for ANF–filling pressure relations. Comparisons between ANF–atrial pressure relations for patients with dilated cardiomyopathy with and without myocarditis were performed using multiple linear regression with an interaction term for patient diagnosis. Statistical calculations were done on an Apple Macintosh computer, using Statview 512+ software. Binomial confidence intervals were based on tables using exact calculations.[29]

RESULTS

Patients: Of the 68 patients in the cardiomyopathy study, 15 (22%) had myocarditis, 5 (7%) had borderline myocarditis, and 48 (71%) had dilated cardiomyopathy without myocarditis. The incidence of myocarditis in the total patient population (n = 82) was 24%. Patients with dilated cardiomyopathy with and without myocarditis had similar degrees of heart failure both at presentation and at time of biopsy and of left ventricular dysfunction demonstrated by depressed cardiac and left ventricular stroke work indexes (Table I). Age and gender distributions, mean hemodynamic data and ANF concentrations are provided in Table I.

Impact of myocarditis on atrial natriuretic factor–filling pressure relations: Figures 1 and 2 are plots of right atrial plasma ANF concentration versus pulmonary arterial wedge and right atrial pressures, respectively, in patients with dilated cardiomyopathy with and without myocarditis. The myocarditis group included patients with borderline myocarditis. From the data in both figures, significant correlations were derived between ANF and left or right atrial pressure (Table II). Although the distributions of pulmonary arterial wedge pressure were comparable between patients with and without myocarditis (Figure 1), only 1 patient with myocarditis had a right atrial pressure ≥8 mm Hg (Figure 2). This patient's biopsy specimen contained myocyte necrosis. Over the range of right atrial pressure <8 mm Hg, the distribution of pressure was comparable for patients with and without myocarditis. Linear regression calculations were performed excluding an outlier point with a highly elevated wedge pressure, right atrial pressure and ANF that could inflate the apparent strength of the relations (Figures 1 and 2).

Multiple linear regression calculations were performed to test for an independent influence of myocarditis on ANF–atrial pressure relations. For both pulmonary arterial wedge pressure ($p = 0.88$) and right atrial pressure ($p = 0.33$, restricted to <8 mm Hg), myocarditis had no significant effect on these relations. The analysis for the right atrial pressure relation was performed excluding patients with pressure ≥8 mm Hg because there was only one patient with myocarditis in that range, providing inadequate information to justify extrapolation of the comparison in that region. Statistical testing performed excluding the 5 patients with borderline myocarditis also failed to demonstrate an alteration in ANF–cardiac filling pressure relations attributable to myocarditis ($p = 0.87$ and $p = 0.47$ for interaction terms for wedge pressure and right atrial pressure relations, respectively). This lack of influence permitted pooling of the data, and the results of individual and pooled linear regression analyses are provided in Table II. The regression slope for patients with right atrial pressure <8 mm Hg was higher than that derived

TABLE I Patient Hemodynamic Data and Atrial Natriuretic Factor Concentrations

	Dilated Cardiomyopathy		
	Without Myocarditis	With Myocarditis	Transplant Recipients
No. of patients	48	20	34
Men/women	29/19	12/8	28/6
Age (year)	49 (14)	39 (13)	47 (10)
NYHA (presentation)	3.3 (0.6)	3.3 (0.8)	
NYHA (biopsy)	2.6 (0.6)	2.2 (0.7)	
RAP (mm Hg)	5 (5.2)	3 (3.8)	5 (4.1)
PAWP (mm Hg)	14 (8.8)	10 (9.2)	9 (6.4)
ANF (pg/ml)	207 (131)	157 (117)	168 (83)
CI (liter/min/m²)	2.3 (0.6)	2.6 (0.6)	2.4 (0.7)
LVSWI (g-m/m²)	30 (12)	33 (14)	36 (12)

All data expressed as mean ± standard deviation.

ANF = atrial natriuretic factor; CI = cardiac index; NYHA = New York Heart Association classification; PAWP = pulmonary arterial wedge pressure; RAP = right atrial pressure; LVSWI = left ventricular stroke work index (normal range 50 to 62 g-m/m²).

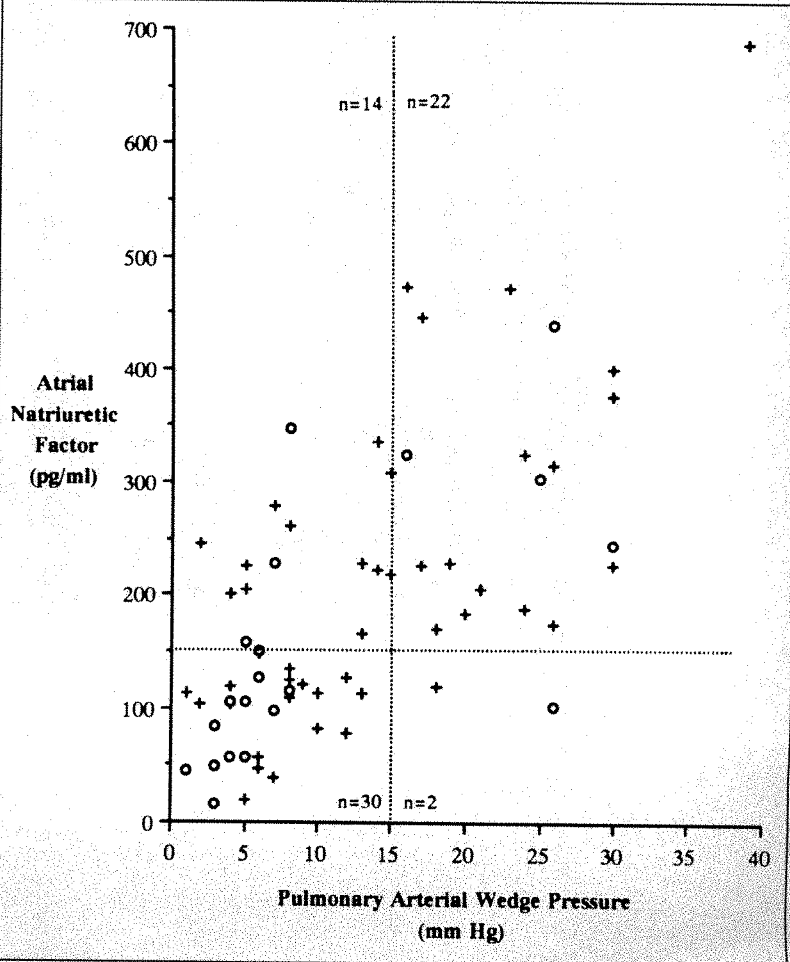

FIGURE 1. Plot of atrial natriuretic factor versus pulmonary arterial wedge pressure in patients with dilated cardiomyopathy. Symbols represent the following patient groups: (○) = myocarditis; (+) = nonmyocarditis; *vertical line* divides patients at pressure of 15 mm Hg; *horizontal line* divides at atrial natriuretic factor level of 150 pg/ml. Number of patients in each quadrant (n) are indicated. Atrial natriuretic factor correlated with pulmonary arterial wedge pressure and this relation was not influenced by myocarditis.

TABLE II Linear Regression Coefficients for Atrial Natriuretic Factor–Filling Pressure Relations

	Regression Coefficient (pg/ml/mmHg)	95% Confidence Intervals	p Value
Atrial Natriuretic Peptide Versus Pulmonary Artery Wedge Pressure			
Dilated cardiomyopathy with myocarditis	8.2*	3.4 to 13.0	0.002
Dilated cardiomyopathy without myocarditis	7.8*	4.3 to 11.3	0.0001
Combined group	8.1	5.4 to 10.8	0.0001
Atrial Natriuretic Factor Versus Right Atrial Pressure			
Dilated cardiomyopathy with myocarditis (RAP <8 mm Hg)	33.0†	16.1 to 49.9	0.0007
Dilated cardiomyopathy without myocarditis (RAP <8 mm Hg)	20.6†	5.4 to 35.8	0.009
Combined group (RAP <8 mm Hg)	24.9	13.5 to 36.3	0.0001
Combined group over entire pressure range	13.6	8.5 to 18.7	0.0001

* p = 0.88; † p = 0.33 for multiple regression analysis of independent influence of myocarditis. Regressions calculated excluding an outlier with highly elevated atrial natriuretic factor, pulmonary arterial wedge and right atrial pressures.
Abbreviations as in Table I.

for the entire patient group, although this was not significant as the 95% confidence intervals had substantial overlap.

From the combined dilated cardiomyopathy data (n = 68), which represents the largest series to date, we sought to identify variation from a linear model of the relation between ANF and atrial pressures. Figures 1 and 2 show that most patients with elevated left or right filling pressures had an ANF level ≥150 pg/ml, whereas those with pressures in the normal range had wide variation in ANF concentration. Thus, most of the information in the regression was captured by knowledge of whether the ANF was ≥ or <150 pg/ml. A receiver-operating curve confirmed this cutoff as an optimal dividing point. Ninety-two percent of patients with elevated pulmonary arterial wedge pressure and 100% with high right atrial pressure had ANF ≥150 pg/ml, whereas only 68% of patients with a wedge pressure <15 mm Hg and 56% with right atrial pressure <8 mm Hg had ANF <150 pg/ml (Table III). Thus, a signifi-

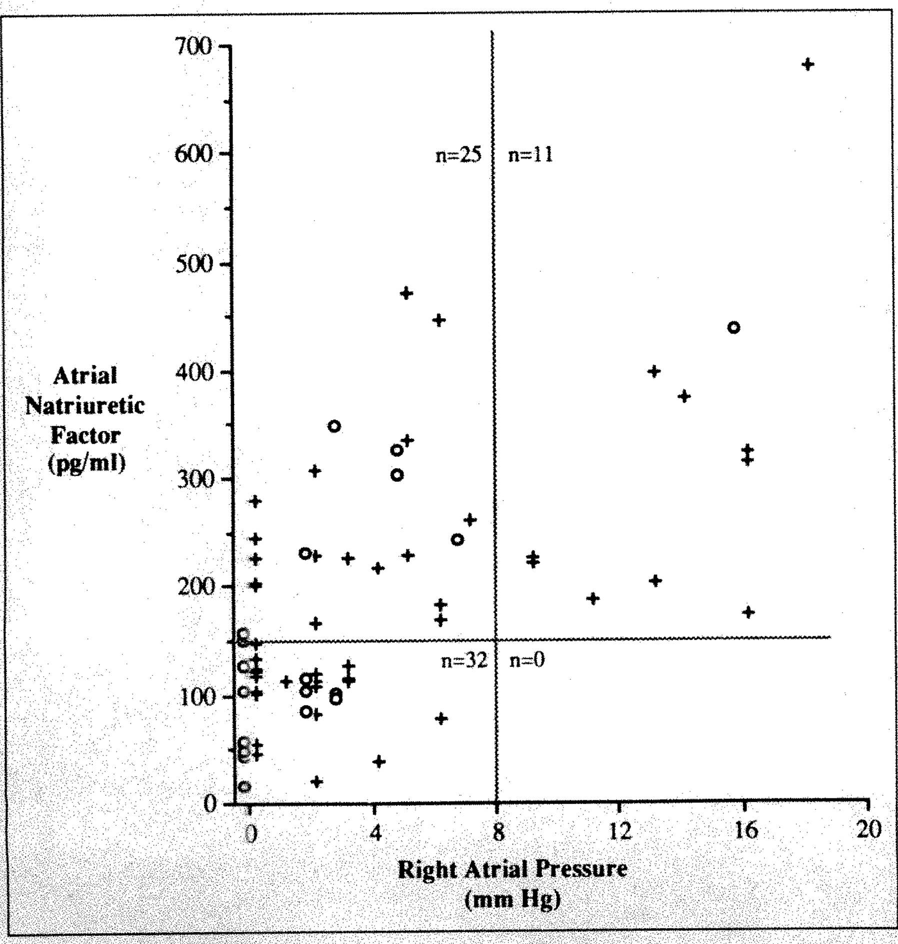

FIGURE 2. Plot of atrial natriuretic factor versus right atrial pressure in patients with dilated cardiomyopathy. Symbols as in Figure 1. *Vertical line* divides patients at pressure of 8 mm Hg; *horizontal line* divides at atrial natriuretic factor level of 150 pg/ml. Number of patients in each quadrant (n) are indicated. Atrial natriuretic factor correlated with right atrial pressure both over the entire range of right atrial pressure and with the range limited <8 mm Hg. Myocarditis had no independent influence over pressure <8 mm Hg.

cant number of patients with cardiomyopathy had elevated circulating ANF despite low filling pressures.

Atrial natriuretic factor in transplant recipients: Although ANF levels were similarly elevated in both the transplant and cardiomyopathy groups (Table I), cardiac transplant recipients did not display a significant correlation between ANF and either wedge pressure ($p = 0.5$, data not shown) or right atrial pressure ($p = 0.29$, Figure 3). The following variables were further examined for possible independent impact on ANF level using multiple regression analysis: degree of transplant rejection, time from transplantation, mean pulmonary artery pressure, right ventricular end-diastolic pressure, mean arterial pressure, cardiac index, dose of immunosuppressive drugs (prednisone, azathioprine and cyclosporin A), or use of diuretics, calcium-channel blockers or angiotensin-converting enzyme inhibitors. None of these factors proved to be significant.

DISCUSSION

The relation between ANF and cardiac filling pressures has been the subject of many investigations. Several studies in small numbers of patients with heart failure have reported statistically significant linear correlations between ANF and right and left heart filling pressures.[10–15] No previous study has examined whether dilated cardiomyopathy, active myocardial inflammation or cardiac transplantation influence this relation.

Studies in a murine myocarditis model have suggested that inflammatory foci might stimulate ventricular ANF synthesis.[16,17] In contrast, immunohistochemical staining of human biopsy specimens has demonstrated fewer ANF containing ventricular myocytes in myocarditis than in dilated cardiomyopathy without myocarditis.[18] In the latter study, however, patients with myocarditis had higher ejection fractions and lower end-diastolic volume indexes than those with dilated cardiomyopathy, making it unclear whether myocardial inflammation could alter ANF level independently of atrial stretch or ventricular pressure overload. In our study, the near equivalence of ANF–pulmonary arterial wedge pressure relation slopes strongly suggests that myocardial inflammation has little to no impact on the coupling of atrial stretch and ventricular pressure overload to circulating ANF. Because the comparison of ANF–right atrial pressure relation slopes was restricted to patients with pressure <8 mm Hg, whether patients with myocarditis and higher right filling pressure would have different circulating ANF remains uncertain. The paucity of patients with myocarditis and elevated right atrial

TABLE III Elevated Atrial Natriuretic Factor Level as a Predictor of High Filling Pressures

	Right Atrial Pressure	Wedge Pressure
Sensitivity (n/n)*	100% (11/11)	92% (22/24)
95% CI	72% to 100%	73% to 99%
Specificity (n/n)*	56% (32/57)	68% (30/44)
95% CI	42% to 69%	52% to 81%

* Calculated using the following cutoffs: right atrial pressure 8 mm Hg, pulmonary arterial wedge pressure 15 mm Hg, atrial natriuretic factor 150 pg/ml.
CI = confidence interval; n = number.

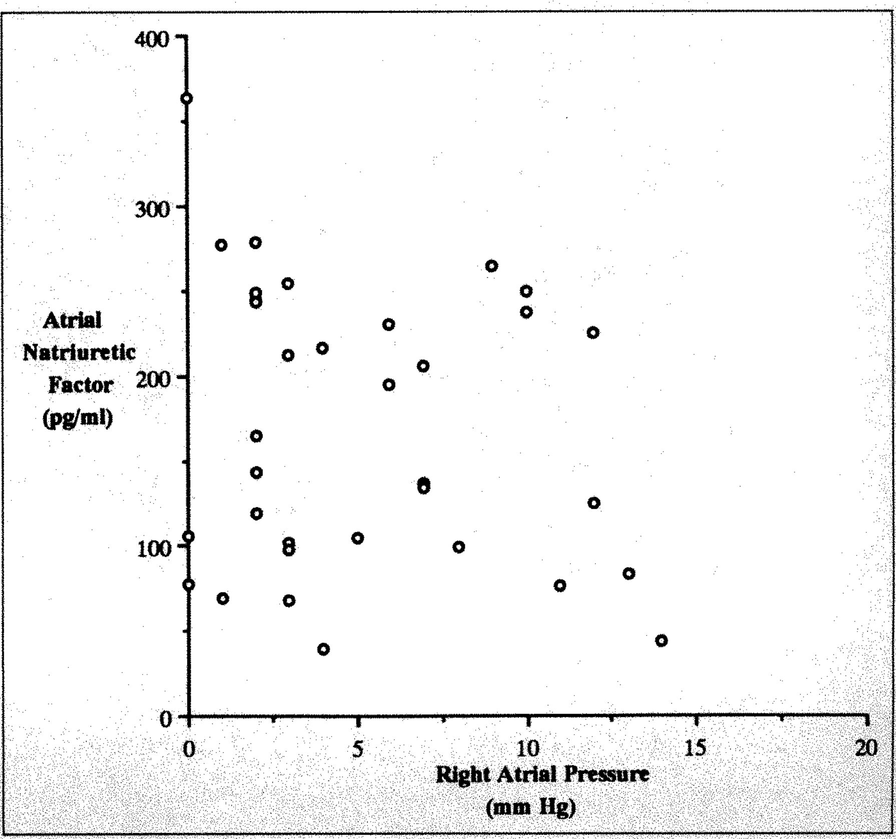

FIGURE 3. Plot of atrial natriuretic factor versus right atrial pressure in heart transplant recipients. There was no significant relation between the 2 variables in this patient group.

pressure could relate to differences in the incidence of biventricular failure or right ventricular compliance.

Whether patients with borderline myocarditis have "true" myocarditis remains controversial. Both an autopsy study[30] and a follow-up biopsy study[31] have shown that a significant number of patients meeting Dallas criteria[26] for myocarditis can have ventricular biopsy specimens showing only borderline myocarditis. In the present study, statistical analysis failed to demonstrate a difference between ANF–filling pressure relations whether or not patients with borderline myocarditis were included. Two factors reduce histologic misdiagnosis: first, multiple biopsy samples per patient minimize sampling error[30]; and second, biopsy samples from patients with dilated cardiomyopathy without myocarditis commonly contain myocyte hypertrophy or interstitial fibrosis.[25,31]

This large group of patients with cardiomyopathy included a significant number of patients with an elevated circulating ANF despite normal filling pressures. Although high left or right intracardiac pressures can increase ANF concentrations, it appears that other factors contribute to elevated ANF in some patients with dilated cardiomyopathy. In neonatal rat ventricles, ANF has been shown to be secreted in a constitutive fashion compared with regulated release from atrial cytoplasmic granules.[32] Both constitutive and granule-mediated ventricular ANF secretion have been demonstrated in the cardiomyopathic hamster.[9] In chronic heart disease, the degree of ventricular ANF synthesis may represent an independent influence on circulating peptide levels.

ANF correlated with neither wedge nor right atrial pressure in cardiac transplant recipients. This observation is consistent with studies in the pithed rat model of cardiac denervation, in which atrial stress failed to stimulate ANF release.[21,22] Vasopressin has been linked to ANF secretion by its ability to restore atrial distention-induced ANF secretion.[22] In cardiac transplant recipients, vasopressin has been shown to be elevated basally and have a blunted increase with volume depletion.[33] Individual transplant recipients have responded to acute increases in filling pressure with increases in ANF level,[34] so that differences in the ANF-release "set-point" among patients may account for the lack of an observed correlation in a population of patients. Whereas denervation, presence of both donor and recipient atria, or abnormalities in circulating hormones, such as vasopressin, are possible causes of such a reset mechanism, our findings suggest that the inflammation of transplant rejection is not involved. Additional work, including measurement of vasopressin and other humoral factors, will be required to elucidate the nature of ANF intracardiac pressure relations in human cardiac transplant recipients.

Two earlier transplant patient studies demonstrated correlations between ANF and atrial filling pressures as well as ANF levels comparable to those reported here.[19,20] Although statistically significant, these relations were modest compared to those in patients with heart failure.[11-15] Both studies had relatively low numbers of patients, and neither graphically presented data nor reported linear regression coefficients, making comparisons to our findings difficult. Although we could not explain the lack of a relation between ANF level and filling pressures on the basis of immunosuppressive or cardiovascular drugs, the number of patients studied and the variability in regimens restrict our ability to rule out a significant drug influence.

The present study was limited by being based on 1 set of hemodynamic conditions per patient and was not designed to assess the relative contribution of the atria and the ventricles to circulating ANF levels. The source and importance of elevated ANF levels in transplant recipients remain to be determined.

We conclude that both left and right atrial filling pressures but not myocardial inflammation are major determinants of circulating immunoreactive ANF concentration in some but not all cardiomyopathic patients. Cardiac transplant recipients, in contrast, display no association between filling pressures and plasma ANF levels, a finding not accounted for by myocardial inflammation secondary to graft rejection, time from transplantation or medical regimens.

Acknowledgment: We are indebted to Ned Kaufman for his technical assistance in performing the ANF radioimmunoassay, to Karen Augustine and Patricia Sullivan for assistance in manuscript preparation, and to Leroy Warthen for preparation of the figures.

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Beneficial Effect of Atrial Pacing in Severe Acute Aortic Regurgitation and Role of M-Mode Echocardiography in Determining the Optimal Pacing Interval

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Jai Patel, MBChB, FCP(SA), and Martin R. Berk, MBBCh, FCP(SA)

The effect of atrial pacing on cardiac performance was assessed in 11 men (aged 20 to 64 years) with recent-onset severe aortic regurgitation (AR), all of whom had diastolic closure of the mitral valve on the echocardiogram. Thermodilution cardiac outputs were determined, and aortic, left ventricular and pulmonary arterial wedge pressures recorded. Once baseline recordings were completed, the pacing rate was increased by increments of 10 beats/min (70, 80, 90 . . .) to a maximal rate of 140 beats/min. The optimal pacing interval, obtained from hemodynamic data, was defined as that at which the lowest filling pressure was associated with the highest cardiac index. This was then compared with a pacing interval derived from the R wave of the electrocardiogram to the diastolic mitral closing point on the M-mode echocardiogram. Such an interval would shorten diastole without affecting forward mitral flow. Atrial pacing improved the overall hemodynamic state in all patients; the most favorable hemodynamics were achieved at heart rates between 110 and 130 beats/min (mean: 120 ± 8). At the optimal rate, left ventricular end-diastolic pressure decreased from 46 ± 7 to 23 ± 12 mm Hg ($p < 0.001$), and the pulmonary arterial wedge pressure from 28 ± 8 to 16 ± 7 mm Hg ($p < 0.001$), while the cardiac index increased from 2.34 ± 0.46 to 2.63 ± 0.49 liters/min/m^2 ($p < 0.01$). The mean difference between the optimal pacing interval determined from the hemodynamic data and the interval derived from the echocardiogram was 18 ± 21 ms. These data suggest that atrial pacing has a predictable, beneficial, hemodynamic effect in patients with acute, severe AR, and that the optimal rate can be predetermined from information obtained from the echocardiogram.

(Am J Cardiol 1991;67:398–403)

The precarious hemodynamics of acute, severe aortic regurgitation (AR) are characterized by marked elevations in left ventricular diastolic pressures, which may exceed that of the left atrium and result in closure of the mitral valve during diastole.[1-5] This pressure phenomenon has been correlated with the M-mode echocardiographic finding of diastolic closure of the mitral valve.[6-9] It is now generally accepted that this echocardiographic feature in patients with recent-onset AR constitutes an indication for early surgery.[8,10,11] Medical treatment has mainly been directed toward "holding" the patient hemodynamically before surgery. Although the medical options are limited,[12] previous studies[9,13,14] suggest that increasing heart rate by atrial pacing may have a beneficial effect on the hemodynamic status of these patients. It is not clear, however, whether these effects are demonstrable in all patients and, if so, at what range of heart rates a predictable hemodynamic improvement might be expected.

Based on our previous observation[9] that the diastolic closure point of the mitral valve has a near constant relation to the preceding R wave of the electrocardiogram, we argued that a pacing interval equal to the interval from the R wave to this closure point on the echocardiogram would increase the heart rate without reducing mitral inflow (Figure 1). This report describes the effect of atrial pacing on the hemodynamics of 11 patients with recent-onset severe AR, all of whom demonstrated closure of the mitral valve in diastole. It further correlates the hemodynamics of the pacing interval predetermined from the M-mode echocardiogram with the optimal pacing interval obtained from hemodynamic measurements at catheterization.

METHODS

Subjects: The clinical and echocardiographic findings of the 11 men, aged 20 to 64 years, with recent-onset severe AR are listed in Table I. The duration of symptoms ranged from 2 to 14 weeks. Although we elected not to study patients with vegetative endocarditis because of the potential risk of embolization during catheterization, 2 patients were evaluated in whom *Streptococcus viridans* was cultured from the blood without demonstrable vegetations on their aortic valve. Except for 2 patients (nos. 10 and 11, Table I) who refused surgery, all others were subjected to valve surgery within 48 hours of cardiac catheterization. One pa-

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tient (no. 8, Table I) included in this study formed part of a previous report.[9]

Echocardiographic examination: M-mode and 2-dimensional echocardiographic recordings were obtained before cardiac catheterization, and were performed with a 90° mechanical sector scanner (Advanced Technology Laboratories, MK5 500 or Ultramark 8 imaging systems) using a 2.25-MHz probe. Diastolic closure of the mitral valve was defined as complete coaptation of the anterior and posterior leaflets at or before the initial inscription of the QRS complex.[7]

Cardiac catheterization: After informed consent, patients underwent cardiac catheterization at which simultaneous aortic, left ventricular and pulmonary arterial wedge pressures were recorded. Pressures were obtained with fluid-filled catheters attached to Hewlett Packard (1290A) transducers. Cardiac output was measured by the thermodilution method through a 7Fr Edwards Swan-Ganz catheter positioned in the pulmonary artery. A 6Fr bipolar pacing catheter was placed in the right atrium for pacing. There were no complications during and after cardiac catheterization in all patients.

Study protocol: Once baseline measurements were completed, atrial pacing was started. The heart rate was increased by increments of 10 beats/min (70, 80, 90 ...), the lowest rate being just faster than the baseline rate, to a maximum of 140 beats/min. After each change in heart rate, a 5-minute stabilization period was allowed before cardiac output was measured and pressures recorded.

1. OPTIMAL PACING INTERVAL: the pacing interval at which the lowest pulmonary arterial wedge and left ventricular end-diastolic pressures were associated with the highest or near-highest cardiac index.

2. R WAVE–MITRAL CLOSURE INTERVAL: the interval between the peak of the R wave of the electrocardiogram and the subsequent point of diastolic mitral closure on M-mode echocardiogram. This interval was used as a measure of the degree by which diastole could be shortened without affecting mitral inflow (Figure 1). This was then compared with the optimal pacing interval by observers who had no prior knowledge of the echocardiographic findings.

Statistical analysis: Results were analyzed using Student's t tests. A p value ≤ 0.05 was considered statistically significant. The dispersion of data is given by the standard deviation and where appropriate by the standard error of the mean. The degree of agreement between the 2 pacing intervals was assessed by constructing plots of the differences against their means.[14]

RESULTS

Echocardiographic features and baseline hemodynamics: The abnormal steady-state hemodynamics and the degree of left ventricular dilatation evident from the internal diameters denote the severity of the volume overload state in the 11 patients (Table I). The marked elevation of left ventricular diastolic pressure, and the crossover between this pressure and the pulmonary arterial wedge pressure in each patient, confirmed the echocardiographic demonstration of diastolic closure of the mitral valve, and underlined the hemodynamic severity of the AR in these patients. The R wave–mitral closure intervals ranged from 450 to 570 ms (mean 520 ± 43 ms). In 5 patients (nos. 1, 5, 8, 10 and 11, Table I) with a tendency toward lower heart rates, aortic diastolic pressures equilibrated with left ventricular diastolic pressures, and this correlated with the echocardiographic demonstration of diastolic opening of the aortic valve.

Hemodynamics with atrial pacing: Rapid atrial pacing improved the overall hemodynamic state in all patients. The mean cardiac index and pulmonary arterial

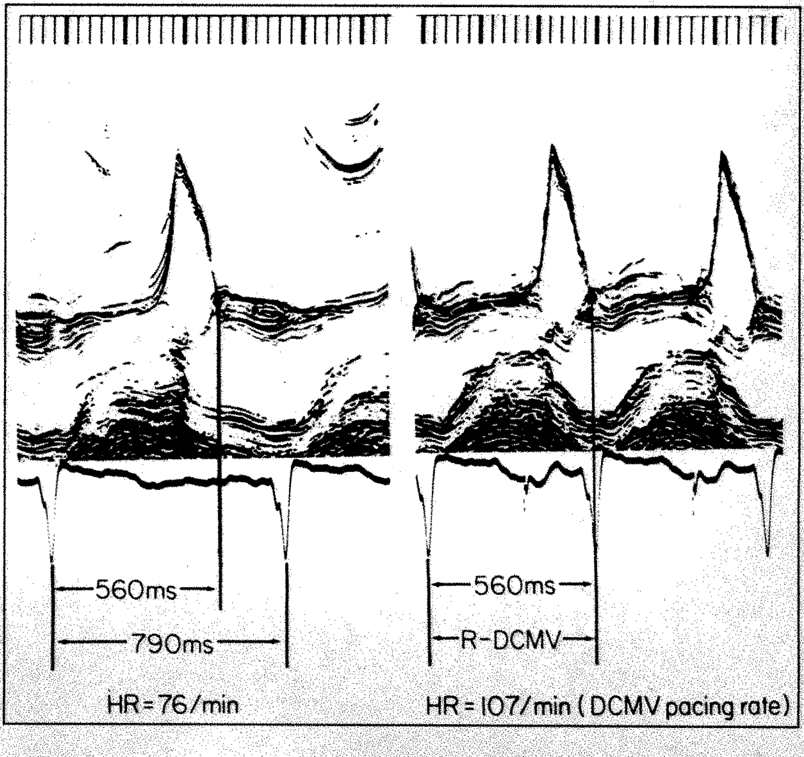


FIGURE 1. M-mode echocardiographic recording of the mitral valve in patient 8 during atrial pacing—the time from the R wave of the electrocardiogram to the diastolic mitral valve closing point (R-DCMV) at a heart rate (HR) of 76 beats/min. At a heart rate of 107 beats/min, diastolic mitral closure did not occur, and this rate was defined as the R wave to mitral closure interval (DCMV pacing rate).

TABLE I Clinical, Echocardiographic and Steady-State Hemodynamic Data in 11 Patients with Recent-Onset Aortic Regurgitation

			Echocardiographic Measurements				Hemodynamics					
Pt.	Age (yr)	NYHA	EDD (mm)	ESD (mm)	%SF	R-DCMV (ms)	HR (beats/min)	Ao (S/D) (mm Hg)	LVEDP (mm Hg)	PAWP (mm Hg)	CI (liters/min/m²)	Aortic Disease
1	37	III	70	50	29	580	83	135/50	50	20	1.92	Prolapsed AV cusps*
2	36	III	68	42	24	490	75	125/50	40	32	2.16	Prolapsed AV cusps*
3	63	III	71	50	30	520	93	140/67	38	18	2.62	Prolapsed AV cusps*
4	20	IV	62	41	34	530	92	85/60	40	22	2.81	Prolapsed AV cusps*
5	33	IV	74	49	34	570	79	130/45	45	30	2.1	Infective endocarditis
6	32	IV	71	40	44	480	93	180/65	55	40	2.53	Infective endocarditis
7	31	III	78	61	22	450	110	165/65	42	22	3.22	Ao anular dilatation
8	23	III	65	42	35	560	76	143/41	43	22	1.7	Syphilitic Ao aneurysm
9	64	III	72	52	27	500	88	140/57	41	32	1.81	Chronic Ao dissection
10	42	III	71	41	42	560	78	145/50	50	32	2.41	Uncertain†
11	46	III	79	61	25	480	88	90/60	60	40	2.43	Uncertain†
Mean ± SD	40 ± 14		71 ± 5	48 ± 8	31 ± 7	520 ± 43	87 ± 10	S = 134 ± 8 D = 54 ± 10	46 ± 7	28 ± 8	2.34 ± 0.46	

* Histology at operation showed myxomatous degeneration of the aortic valve.
† Refused surgery.
Ao = aortic; AV = aortic valve; CI = cardiac index; D = diastolic; EDD = end-diastolic diameter; ESD = end-systolic diameter; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association; PAWP = pulmonary arterial wedge pressure; R-DCMV = interval from R wave of the electrocardiogram to the diastolic closure point of the mitral valve; S = systolic; SD = standard deviation; % SF = shortening fraction.

wedge pressure at each heart rate is shown in Figure 2. The most favorable hemodynamic states were achieved for each patient at heart rates between 110 and 130 beats/min (mean 120 ± 8). Patients 2, 5, 8 and 10 with lower baseline heart rates (<80 beats/min) achieved optimal performance at lower pacing rates (mean 115 ± 5 beats/min). At the optimal pacing interval, the mean left ventricular end-diastolic pressure decreased from 46 ± 7 to 23 ± 12 mm Hg ($p < 0.001$), and the mean pulmonary arterial wedge pressure decreased from 28 ± 8 to 16 ± 7 mm Hg ($p < 0.001$), while the cardiac index increased significantly from 2.34 ± 0.46 to 2.63 ± 0.49 liters/min/m^2 ($p < 0.01$) (Figure 3, A to C). There also was a significant increase in aortic diastolic pressure from 54 ± 10 to 66 ± 12 mm Hg ($p < 0.001$) as well as an increase in the mean aortic pressure from 89 ± 6 to 98 ± 6 mm Hg ($p < 0.001$). At rates above the optimal pacing rate (130 to 140 beats/min), there was a slight increase in pulmonary arterial wedge pressure and a nonsignificant decrease in the cardiac index (Figure 2). A representative example of the effects of atrial pacing on aortic, left ventricular diastolic and pulmonary arterial wedge pressures are shown in Figure 4.

Optimal pacing interval versus R wave–mitral closure interval: The mean difference between the optimal pacing interval defined from the hemodynamic data and the R wave–mitral closure interval was 18 ms and the standard deviation of differences was 21 ms. The distribution of the differences against their mean are shown in Figure 5.

DISCUSSION

The amount of regurgitant flow per stroke through an incompetent aortic valve is largely determined by the regurgitant orifice area, the diastolic pressure gradient between aorta and left ventricle, and the duration of diastole.[10,15] The hemodynamic consequences of this volume load is dependent not only on its magnitude, but also on the rapidity with which regurgitation develops.[10] In acute or subacute AR the ventricle operates on the less compliant portion of the pressure-volume curve; consequently, a slight decrease in regurgitant volume during a shortened diastole may significantly reduce the filling pressure.

Since Corrigan[16] suggested that an increase in heart rate may be advantageous to patients with AR, several investigators[12,13,15,17,18] have addressed the issue and are in agreement about certain aspects but differ in others. Despite the diverse techniques used to measure regurgitant flow, most recent observations[12,15,17] suggest that while the regurgitant volume per stroke decreases, there is little or no change in the regurgitant volume per minute or regurgitant fraction as heart rate is increased. Judge et al[12] demonstrated that atrial pacing is associated with an increase in cardiac output, and a decrease in left ventricular end-diastolic volume and pressure, whereas Firth et al[17] found the cardiac output and pulmonary arterial wedge pressure to be unchanged with pacing, despite a decremental reduction in end-systolic and end-diastolic volumes. In animal models of acute

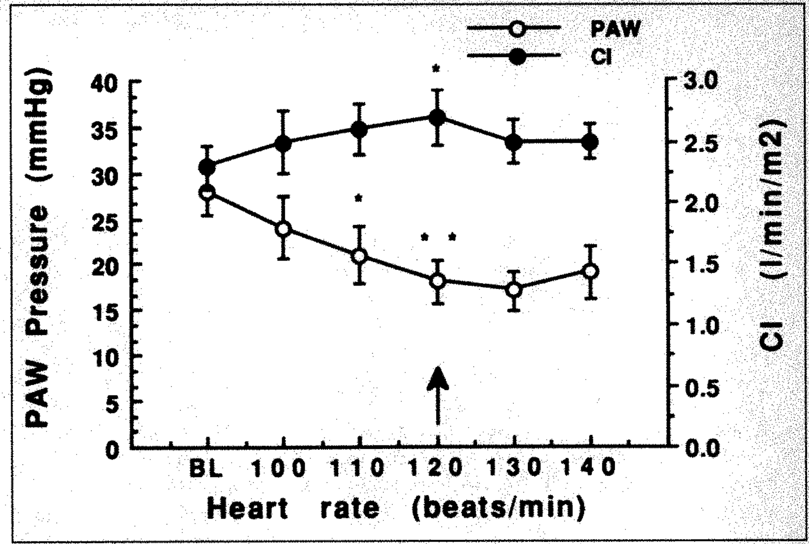
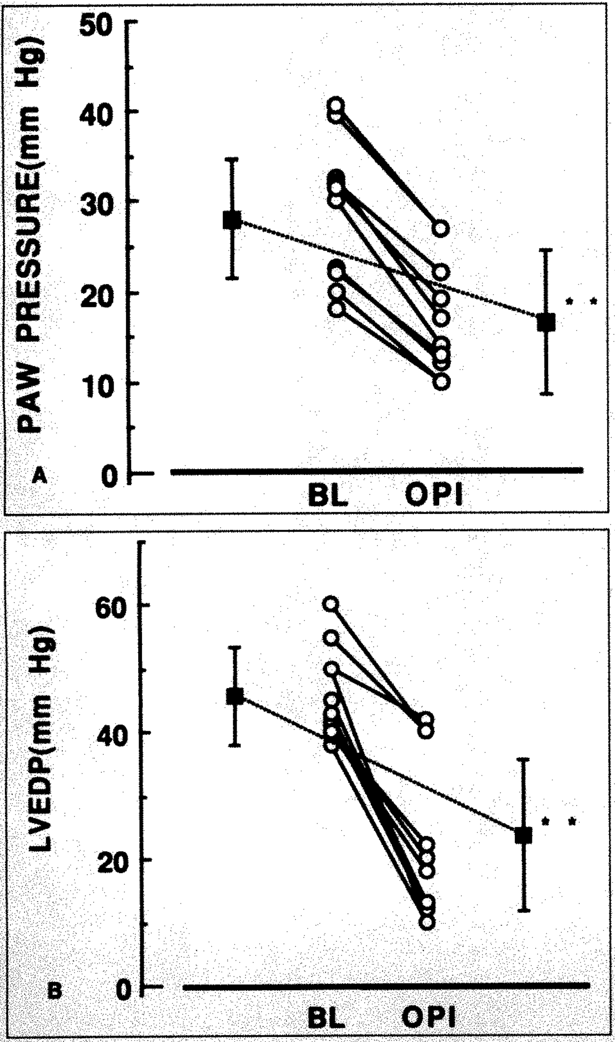


FIGURE 2. Effect of atrial pacing on the mean (± standard error of the mean) cardiac index (CI) and pulmonary arterial wedge (PAW) pressure. *Arrow*, optimal pacing interval. * p <0.01 vs baseline (BL); ** p <0.001 vs baseline.

AR,[13,19] a modest increase in the heart rate was found to decrease left ventricular end-diastolic pressure and increase cardiac output. These disparate observations may be partly explained by the variance in the hemodynamic conditions of the patients studied.



To circumvent the aforementioned problems, a fairly homogeneous patient population was selected based on the demonstration of diastolic closure of the mitral valve, the echocardiographic hallmark of hemodynamically severe AR. We believed that this subset of patients would be the most likely to benefit from a more rapid rate. The shortening characteristics and the degree of left ventricular dilatation apparent from the internal diameters, as well as the relatively low steady-state heart rates in most patients (Table I), are somewhat surprising and suggest that the AR was either subacute or acute in most patients. The rate at which the ventricle dilates in response to a significant volume load, however, may be much more rapid than generally accepted. In an animal model of AR, Belenkie and Rademaker[19]

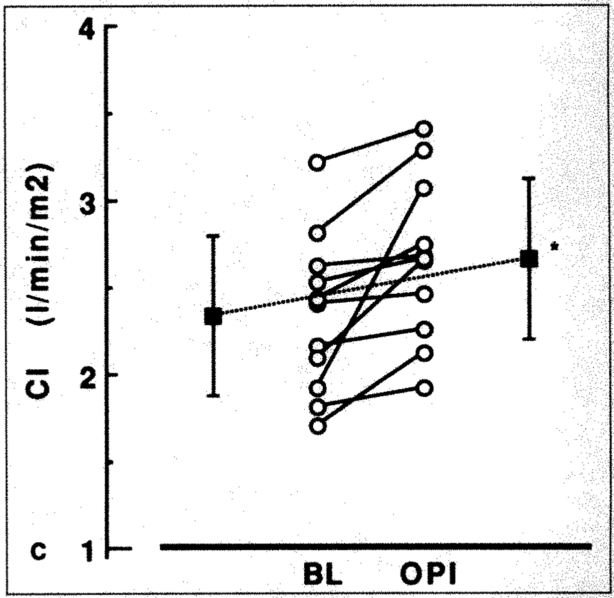


FIGURE 3. *A to C*, the effect of atrial pacing at the optimal pacing interval (OPI) on the pulmonary arterial wedge (PAW) pressure in *A*, left ventricular end-diastolic pressure (LVEDP) in *B*, and cardiac index (CI) in *C*. The data are compared with baseline (BL) values. Data are expressed as mean ± standard deviation. * p <0.01 vs baseline and ** p <0.001 vs baseline.

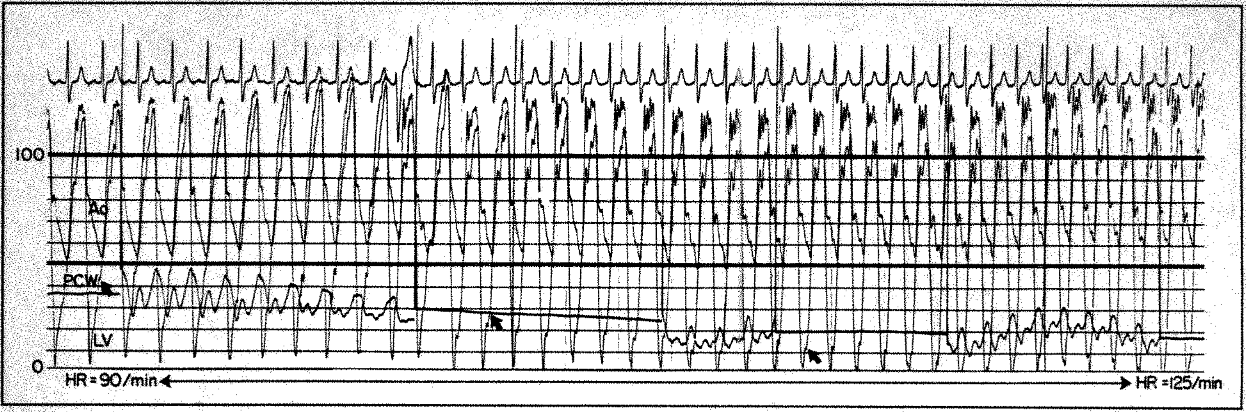


FIGURE 4. Simultaneous pressure recording (paper speed 25 mm/s) of aortic (Ao), left ventricular (LV) and pulmonary capillary wedge (PCW) pressure in patient 10 during atrial pacing. A progressive decrease in LVEDP (*thick arrows*) and PCW pressure and an increase in the aortic systolic pressure occurred when heart rate (HR) was increased from 90 to 125 beats/min.

found a rapid increase in the end-diastolic and end-systolic diameters over a period of 80 days from the onset of AR, after which the diastolic diameters increased more slowly. Despite not having hyperacute AR, a consistent and profound decrease in both left ventricular end-diastolic and pulmonary arterial wedge pressures, together with a significant increase in the cardiac index, was seen in all patients when there was a modest increase in heart rate (120 ± 8 beats/min). At heart rates of 130 to 140 beats/min, there was a slight decrease in the cardiac index as well as an increase in pulmonary arterial wedge pressure (Figure 2). The changes in filling pressure induced by pacing in this study differ from those of Firth et al,[17] but are in agreement with those of Judge et al,[12] and comparable to the results obtained in dogs.[13] The increase in cardiac index with pacing was less impressive than some of the other studies.[14,18]

Defining a heart rate at which the best overall improvement in hemodynamics can be expected from the published data is complicated by the nonuniformity of the pacing protocols used.[13,15,17,18] In an intraoperative study, Brawley and Morrow[15] found that the total forward, regurgitant and net forward flows were maximal at heart rates between 80 and 120 beats/min. Although Firth et al[17] did not find any change in the pulmonary arterial wedge pressure at heart rates ranging from 72 to 120 beats/min, an increase was observed when pacing was continued at 140 beats/min. After producing acute reversible AR, Laniado et al[13] showed a reduction in left atrial pressures at heart rates from 90 to 120 beats/min but an increase in pressure at a heart rate of 150 beats/min. They defined the optimal rate as the rate at which diastole could be shortened without affecting mitral flow.

To be more confident about the range of heart rates where hemodynamic improvement may be observed, we paced at 6 designated rates (90 to 140 beats/min). The best hemodynamic responses to pacing were shown at heart rates about 35 to 40 beats/min (mean 120 ± 8) above baseline rates, and are similar to those observed by other investigators.[12,13] The most favorable pacing interval defined by the hemodynamic responses was then compared with the R wave–mitral closure interval. The relatively small differences between these intervals

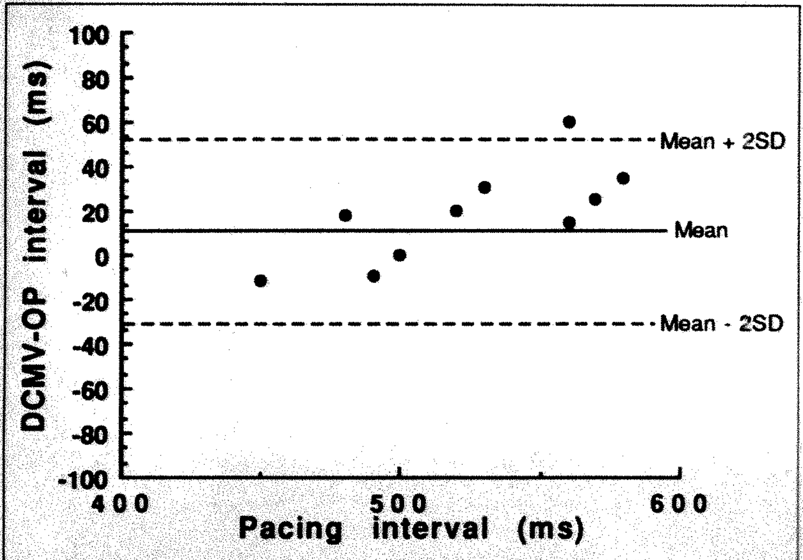


FIGURE 5. This Bland Altman plot shows the distribution (mean ± 2 standard deviation [SD]) of the differences between the R wave to mitral closure (DCMV) and optimal pacing (OP) interval against the mean difference.

suggest that the interval predetermined from the echocardiogram is an adequate predictor of the ideal pacing interval (Figure 5).

Study limitations: There are several limitations to this study. Although atrial pacing is effective in improving the hemodynamic state of these patients, it was not compared to other, more conventional, forms of medical treatment, such as pre- and afterload reduction. A recent observation suggests that intravenous nitroglycerin may also be effective in improving the hemodynamics of acute AR.[20] The hemodynamic advantage of abbreviating diastole, and thus reducing the regurgitant volume per stroke, with incremental pacing in AR, is to some extent negated by the concomitant increase in aortic pressure. It would have been useful to establish whether this increase in regurgitant gradient during atrial pacing could have been attenuated by the introduction of a peripheral vasodilator. Finally, as we did not perform echocardiographic examinations during cardiac catheterization, we were unable to characterize the effect of atrial pacing on the pressure-dimension relations of the left ventricle in this condition, which would have shed some light on the effect of pacing on left ventricular end-diastolic volumes and its relation to the ideal pacing interval.

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Simultaneous Occurrence of Mitral Valve Prolapse and Systolic Anterior Motion in Hypertrophic Cardiomyopathy

Julio A. Panza, MD, and Barry J. Maron, MD

This report describes the simultaneous occurrence of mitral valve prolapse (MVP) and systolic anterior motion (SAM) in hypertrophic cardiomyopathy (HC). In 25 patients (aged 7 to 62 years, mean 29), 15 (60%) of whom were male, distal portions of the anterior or posterior mitral leaflets approached or made midsystolic contact with the ventricular septum, whereas the proximal portion of the mitral leaflets showed marked cephalad excursion into the left atrium, 5 to 15 mm beyond the mitral anular plane. Three mitral valves that were available for gross visual inspection were not morphologically typical of patients with primary MVP. Clinical features and natural history (1 to 14 years [mean 6] of follow-up), cardiac dimensions, and distribution of left ventricular hypertrophy defined in the study patients did not appear to differ distinctly from those in the overall referral population of patients with HC evaluated at our institution. Hence, patients with HC may show a striking pattern of mitral valvular motion involving SAM into the left ventricular outflow tract, as well as MVP; this prolapse motion is probably due to anatomic disproportion between the mitral valve and the small left ventricular cavity rather than to the coexistence of 2 separate disease entities. Such patients further define the great diversity evident within the broad clinical spectrum of HC.

(Am J Cardiol 1991;67:404–410)

Hypertrophic cardiomyopathy (HC) is a primary cardiac disease characterized by a broad clinical and pathologic spectrum, including patients with and without obstruction to left ventricular outflow.[1-3] Although the mitral valve is responsible for dynamic subaortic obstruction by virtue of systolic anterior motion (SAM) and apposition to the ventricular septum,[4-6] the mitral leaflets have often been described at necropsy as free of intrinsic disease.[7,8] Mitral valve prolapse (MVP) is a relatively common clinical entity that may be a manifestation of a primary disease in which there is a congenital structural abnormality of the mitral valve,[9-11] or that, alternatively, can occur with a structurally normal valve as a consequence of other cardiac conditions associated with a small left ventricular cavity or distorted ventricular geometry.[12-14] In our experience, systolic MVP is uncommon in patients with HC. Consequently, identification of several patients with HC and unique mitral valvular dynamics, involving striking and unequivocal MVP and SAM, suggested the potential importance of analyzing in detail the clinical and echocardiographic features of this subgroup of patients.

METHODS

Patient selection: Between 1979 and 1988, 1,230 patients with HC were studied with echocardiography in the National Heart, Lung, and Blood Institute. Of these, 25 (2%) were included in this study because they met the following criteria: a distinctive pattern of systolic motion of the mitral valve on the 2-dimensional echocardiogram with marked cephalad displacement of the proximal portion of the valve into the left atrium (as visualized in the apical or parasternal long-axis views, or both) and simultaneous anterior motion of the distal portion toward the ventricular septum. Because it has been shown that normal subjects may show mild systolic displacement of the mitral leaflets only in the apical 4-chamber view, merely as a consequence of the geometric characteristics of the mitral valvular plane,[15] systolic protrusion of the leaflets into the left atrium was not considered evidence of MVP unless the leaflet displacement beyond the mitral anulus was ≥5 mm.[15] HC was diagnosed by echocardiographic demonstration of an asymmetrically hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease.[2]

At initial evaluation, the 25 study patients were aged 7 to 62 years (mean 29); 7 were <20 years and 5 were

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>40 years of age. Fifteen patients (60%) were men and 10 (40%) were women. No patient had a history of infective endocarditis or rheumatic fever, or evidence of rheumatic heart disease.

Two-dimensional echocardiography: An Advanced Technology Laboratory Mark 500 mechanical sector scanner with a 3-MHz transducer or a Hewlett-Packard (Sonos 500) real-time, phased-array, 90° sector scanner with a 2.5-MHz transducer was used to obtain 2-dimensional echocardiograms. Real-time studies were recorded at 60 frames/s.

Two-dimensional images were obtained in a number of cross-sectional planes by using standard transducer positions. Magnitude of MVP was assessed by measuring the maximal distance between the plane of the mitral anulus and the most cephalad mitral valve echoes during systole in the parasternal long-axis and apical 4-chamber views. Distribution of left ventricular hypertrophy was assessed, as previously described,[16] by an integration of observations in multiple cross-sectional planes.

To define the sequence of events that characterized the motion of the mitral valve during systole, 3 consecutive beats of sufficient technical quality were selected from the real-time 2-dimensional images in each patient to allow frame-by-frame analysis of dynamic events—i.e., onset of SAM, of mitral-septal contact or maximal SAM, and of MVP beyond the mitral anular plane. Timing was assessed by establishing the number of frames between the R wave of the electrocardiogram and each valvular event. Intervals measured in 3 cycles were averaged for each patient.

M-mode echocardiography: M-mode echocardiograms were derived from the 2-dimensional image under direct anatomic visualization. Cardiac dimensions were assessed according to the criteria of the American Society of Echocardiography.[17] Mitral valve position index was calculated by dividing the distance between the mitral valve and the posterior free wall endocardium by the distance between the mitral valve and the septal endocardium.[18] Left ventricular outflow tract transverse dimension was measured as the distance between the mitral valve and septal endocardium, at the point of valve leaflet closure.[18]

Degree of posterior mitral valve bowing was measured during systole as the distance between the most posterior mitral valve echo and the hypothetical C-D line.[19] Redundancy of mitral valve leaflets was assessed by measuring the thickness of mitral valve echoes in diastole at the midpoint of the E-F slope.[20] In patients who had not undergone cardiac catheterization, basal subaortic pressure gradient was estimated by the magnitude and duration of SAM[4] or by continuous-wave Doppler interrogation of outflow velocities, or both.

RESULTS

Left ventricular morphology: An asymmetric pattern of left ventricular hypertrophy was identified in each patient. Wall thickening was confined to the anterior ventricular septum in 7 patients, involved both the anterior and posterior ventricular septum (but not the left ventricular free wall) in 6, and diffusely involved substantial portions of both the septum and anterolateral free wall in 9. The remaining 3 patients showed more unusual patterns of hypertrophy with thickening of posterior septum and contiguous free wall (2 patients) or only anterolateral free wall (1 patient).[21] Maximal left ventricular wall thickness (usually of the anterior septum) ranged from 15 to 33 mm (mean 21).

Left ventricular end-diastolic cavity dimensions were 28 to 50 mm (mean 38) and end-systolic dimensions were 12 to 35 mm (mean 20). Both were reduced (<95% prediction interval)[22] in 20 patients and normal in 5. In each patient, transverse outflow tract dimension at end diastole was reduced (range 10 to 25 mm, normal >30), and the mitral valve was positioned anteriorly within the ventricular cavity (mitral valve position index 0.4 to 1.3, normal <0.3). Left atrial dimension was 24 to 70 mm (mean 40) and was >45 mm in 7 patients.

Mitral valve appearance and motion: Each of the 25 patients showed a distinctive mitral valvular motion pattern characterized by systolic protrusion into the left atrium as well as by SAM into the left ventricular outflow tract (Figures 1 to 5). Systolic displacement of a portion of the valve was identified well beyond the mitral anular plane for a distance of 5 to 15 mm (mean 8) (Figures 1 to 3); prolapse was evident in the apical 4-chamber view in all 25 patients, and also in the parasternal long-axis view in 15 patients (Figure 4).

SAM was marked and resulted in apposition of the mitral valve and ventricular septum in 19 of 25 patients (prolonged in 11 and brief in 8) and was mild to moderate in the remaining 6 patients (Figure 5); of these latter 6 patients, minimal systolic distance between the mitral valve and septum was <10 mm in 2 and ≥10 mm in the other 4. There was no evidence of flail mitral valvular motion, ruptured chordae tendineae or prolapse of the tricuspid valve.

Frame-by-frame analysis of mitral valvular motion more precisely defined the sequence of events. In early systole (85 ± 34 ms after R wave on electrocardiography), distal portions of anterior and posterior mitral leaflets began to move in concert toward the septum, often with the anterior leaflet bending acutely. As tips of the leaflets approached the septum, more proximal portions moved abruptly cephalad, prolapsing into the left atrium (130 ± 45 ms after R wave). Mitral-septal contact (or maximum SAM) occurred at 165 ± 42 ms after R wave. The maximal degree of MVP was achieved later in systole at 285 ± 72 ms after R wave. In each patient, the onset of MVP occurred before maximal SAM of the mitral valve (Figures 1 to 3).

In 20 of 25 patients, SAM was produced predominantly by the distal portion of anterior leaflet (which made contact or most closely approached the septum because of its anterior anatomic position) (Figures 1 and 2), although the posterior leaflet also participated in this anterior motion in 16 patients. In the 20 patients, the systolic MVP was largely produced by anterior leaflet alone (14 patients) or in combination with posterior leaflet (6 patients) (Figures 1 and 2). In the other 5 patients, the posterior leaflet alone was responsible for SAM,[23] while the anterior leaflet prolapsed into the left atrium (Figure 3).

On M-mode echocardiography, only 2 of 25 study patients showed systolic MVP beyond the hypothetical C-D line (pansystolic bowing of 2 and 8 mm). Thickness of mitral leaflets[20] was 3 to 5 mm in 21 patients and was increased (>5 mm) in only 1 (8 mm).

Hemodynamic characterization: Fifteen of the 25 patients underwent cardiac catheterization within 1

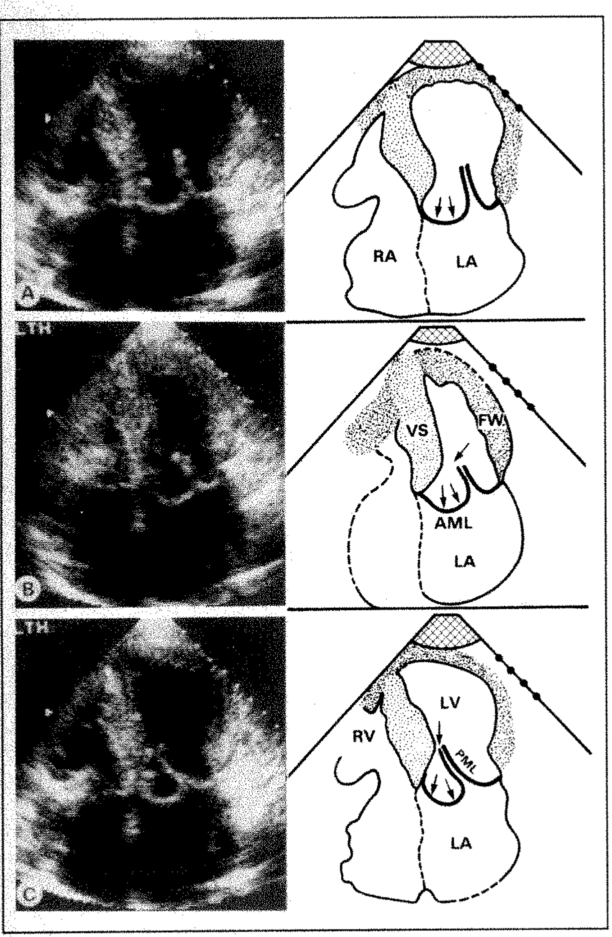

FIGURE 1. Two-dimensional echocardiographic stop-frame images *(left)*, accompanied by schematic illustrations *(right)*, obtained during the same cardiac cycle in the apical 4-chamber view from a 24-year-old patient with obstructive hypertrophic cardiomyopathy. *A*, at onset of systole, anterior and posterior mitral leaflets have coapted; the proximal portion of the anterior leaflet protrudes slightly into the enlarged left atrium (LA) *(double arrows)*; the occurrence of mitral valve prolapse before systolic anterior motion shown here differs from most other study patients. *B*, distal portions of both the anterior (AML) and posterior mitral leaflets move toward the ventricular septum (VS) *(single arrow)*, while the proximal anterior leaflet prolapses further beyond the mitral anular plane *(double arrows)*. *C*, the distal anterior leaflet bends acutely and contacts the septum *(single arrow)*, producing obstruction of left ventricular outflow; marked mitral valve prolapse of the anterior leaflet well beyond the anular plane (i.e., 12 mm) *(double arrows)* is also present, giving the AML the appearance of folding upon itself. FW = left ventricular free wall; LV = left ventricle; PML = posterior mitral leaflet; RA = right atrium; RV = right ventricle. Calibration dots are 1 cm apart in all echocardiographic frames.

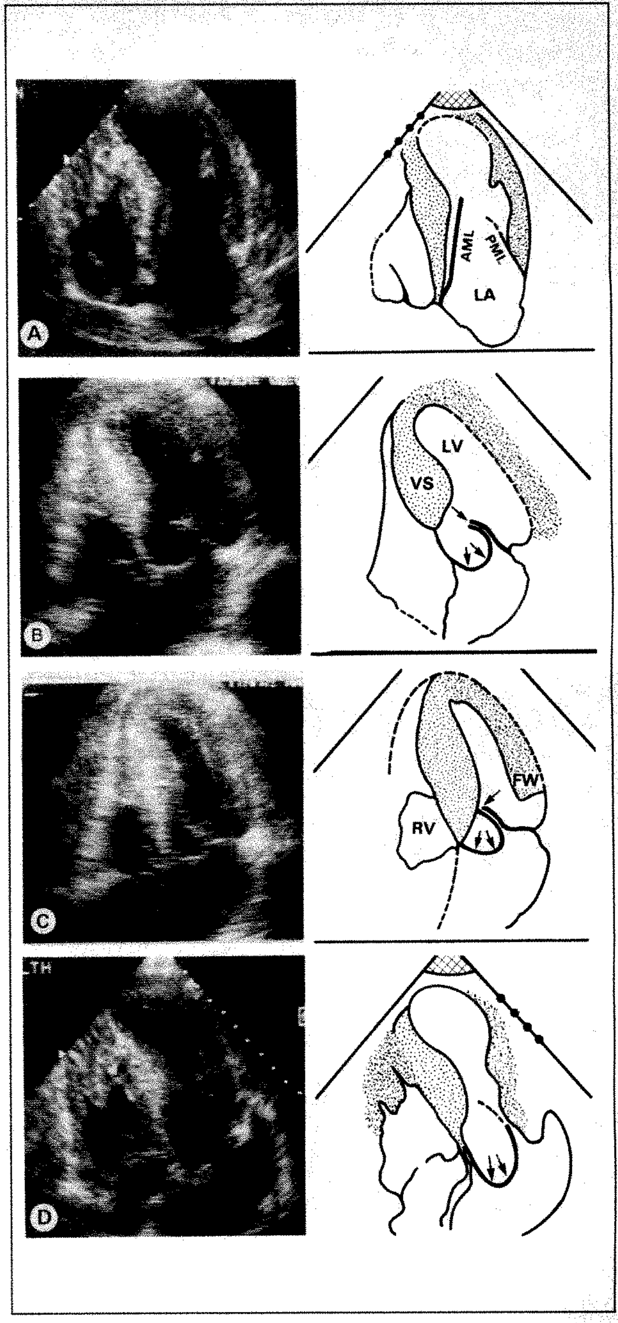

FIGURE 2. Sequential 2-dimensional echocardiographic stop-frame images *(left)*, accompanied by schematic illustration *(right)*, obtained during the same cardiac cycle in the apical 4-chamber view from a 20-year-old man with obstructive hypertrophic cardiomyopathy. *A*, end diastole; *B*, *C* and *D*, systole. *A*, mitral valve is open and both the anterior (AML) and posterior mitral leaflet (PML) appear elongated in the basal-apical plane. *B*, distal portions of mitral leaflets approach the ventricular septum (VS) with the AML bending acutely *(single arrow)* while the proximal portion of the AML begins to protrude into the left atrium *(double arrows)*. *C*, in sequential systolic frame, the distal AML tip makes midsystolic contact with the septum *(single arrow)*, producing dynamic obstruction of left ventricular outflow; the proximal portion of the leaflet extends well beyond the mitral anular plane (i.e., up to 15 mm) *(double arrows)*. *D*, with slight transducer angulation, the maximal degree of AML prolapse into the left atrium is identified *(double arrows)*, although the distal margins of the mitral leaflets are not well visualized in this plane. FW = left ventricular free wall; LV = left ventricle; RV = right ventricle.

year of their initial evaluation. Thirteen of these 15 had a left ventricular outflow gradient ≥30 mm Hg (range 45 to 145) under basal conditions (9 patients) or with provocation maneuvers such as Valsalva maneuver, amyl nitrite inhalation or isoproterenol infusion (4 patients); the other 2 patients had no basal gradient and only small gradients with provocation (20 mm Hg and 25 mm Hg). Maximal outflow gradients recorded during catheterization in the 15 patients were 20 to 140 mm Hg (average 85).

Of the 10 patients who did not undergo cardiac catheterization, 6 showed marked SAM with prolonged mitral-septal contact (and Doppler peak outflow velocities 3.2 to 4.7 m/s) and were therefore judged to have outflow obstruction under basal conditions.[4] Hence, 19 of the 25 study patients (76%) had evidence of substantial obstruction to left ventricular outflow either at cardiac catheterization or by echocardiography.

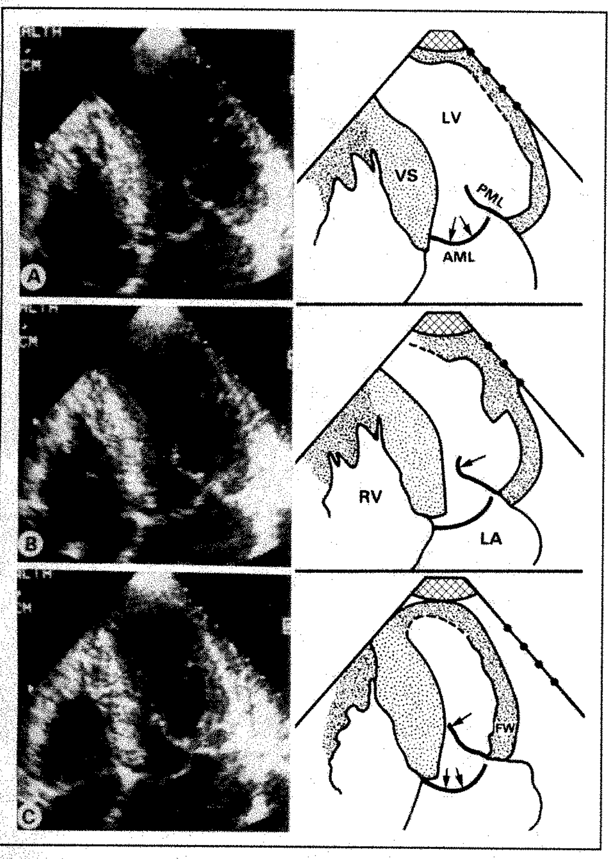

FIGURE 3. Sequential stop-frame echocardiographic images *(left)*, accompanied by schematic illustrations *(right)*, obtained during systole in the apical 4-chamber view from a 35-year-old woman with hypertrophic cardiomyopathy. *A*, at the onset of systole, the mitral leaflets fail to coapt normally at their distal margins; at mitral closure, the anterior mitral leaflet (AML) contacts the base of the posterior mitral leaflet (PML) and the "residual" portion of the PML distal to the site of coaptation protrudes into the left ventricular outflow tract and approaches the ventricular septum (VS), resulting in a subaortic gradient of 80 mm Hg. The AML also bows toward the left atrium *(double arrows)*. *B*, in subsequent midsystole, the PML more closely approaches the septum *(arrow)* and the AML protrudes into the left atrium (LA). *C*, the PML contacts the septum *(arrow)*, producing obstruction to left ventricular outflow, and the AML prolapses into the LA *(double arrows)*. FW = left ventricular free wall; LV = left ventricle; RV = right ventricle.

In the 15 study patients who underwent cardiac catheterization, left ventricular end-diastolic pressure ranged from 10 to 40 mm Hg (mean 19) and was >20 mm Hg in 8 patients. Mitral regurgitation was identified by left ventricular angiography in 11 of the 15 patients (mild in 6 and moderate-to-severe in 5).

Electrocardiography: The 12-lead electrocardiography was abnormal in 24 of the 25 patients. A wide variety of alterations were observed, but no single pattern was characteristic of the overall study group. Most frequently observed abnormalities were left ventricular hypertrophy (21 patients), ST segment and T-wave alterations (13 patients), and abnormal Q waves (12 patients). A variety of conduction defects were relatively common (9 patients), including 1 patient with complete heart block.

Ambulatory electrocardiography: Ambulatory 24-hour electrocardiographic monitoring was performed in

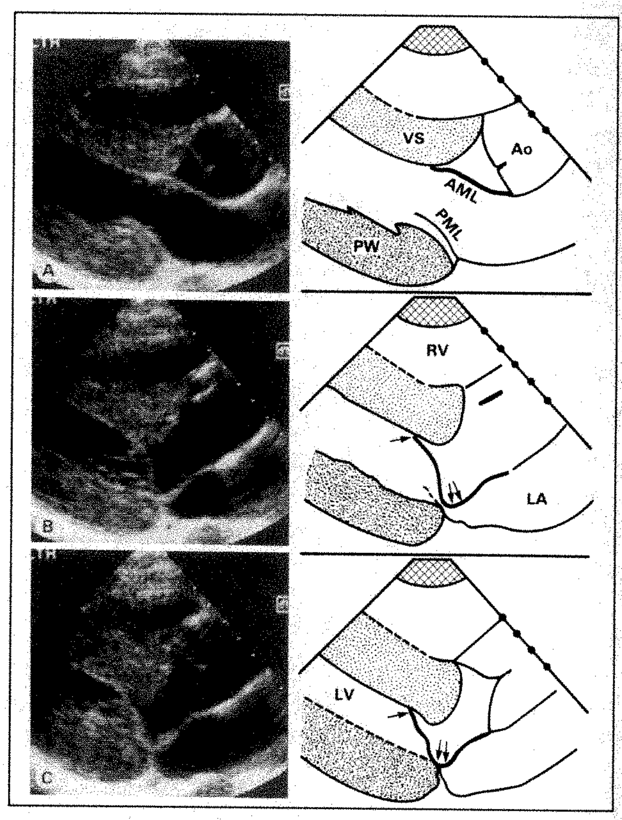

FIGURE 4. Sequential 2-dimensional echocardiographic stop-frame images *(left)*, accompanied by schematic illustrations *(right)*, obtained during the same cardiac cycle in the parasternal long-axis view from the same patient shown in Figure 1. *A*, end diastole; *B* and *C*, systole. *A*, mitral valve is open and the anterior mitral leaflet (AML) appears markedly elongated. *B* and *C*, during the subsequent systole, the distal portion of the AML bends almost 90° anteriorly and makes contact with the ventricular septum *(single arrow)*, while the base of the leaflet protrudes into the left atrium (LA) *(double arrows)*. Note the systolic preclosure of the aortic valve in *C*, a consequence of dynamic subaortic obstruction produced by mitral systolic anterior motion. Ao = aorta; LV = left ventricle; PML = posterior mitral leaflet; PW = posterior wall; RV = right ventricle; VS = ventricular septum.

20 patients (while they were not receiving cardioactive drugs). Clinically relevant arrhythmias were identified in 9 of these, including paroxysmal atrial fibrillation in 6 patients (1 subsequently incurred a cerebrovascular accident), nonsustained ventricular tachycardia in 2 and sinus arrest and junctional escape beats in 1 (an electrophysiologic study documented sinus node dysfunction).

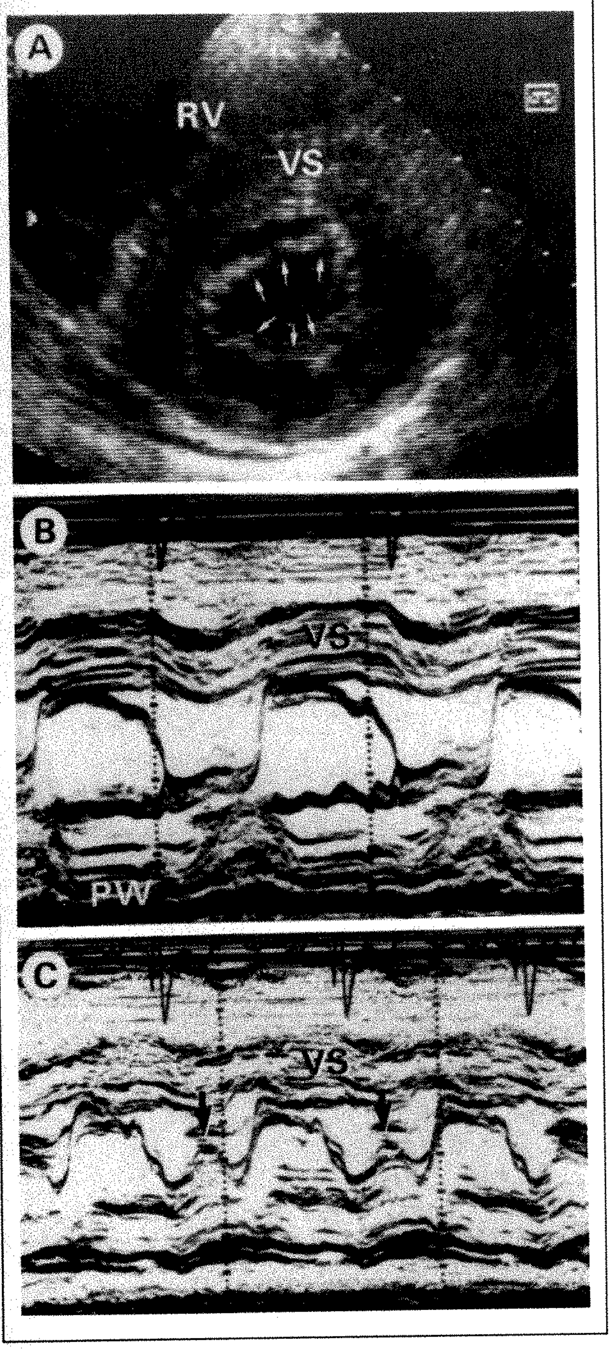

FIGURE 5. *A*, stop-frame echocardiographic image in the parasternal short-axis view at end diastole and 2 M-mode recordings *(B* and *C)* obtained at different mitral valve levels from the same patient shown in Figure 3. *A*, anterior ventricular septum (VS) is mildly thickened; prominent mitral valve *(arrows)* appears large relative to left ventricular cavity size. *B*, mitral valve appears large and does not show systolic anterior motion. *C*, from a most distal transverse plane of the mitral valve, where mild systolic anterior motion is evident *(arrows)*. PW = posterior wall; RV = right ventricle.

Clinical findings and follow-up: On physical examination, 24 of the 25 patients had a grade 2 to 3/6 systolic ejection murmur; however, in none was the murmur judged to be late-systolic. A midsystolic click was reported in only 2 patients. Patients experienced a wide variety of symptoms, including exertional dyspnea (12 patients), chest pain (11 patients), fatigue (10 patients), palpitations (8 patients) and syncope (3 patients).

Twenty-two of the 25 patients had a longitudinal follow-up of ≥1 year (mean 6, maximum 14) after their initial evaluation at our institution. Fifteen patients were either asymptomatic or mildly symptomatic at initial evaluation; 14 of these were unchanged at their most recent evaluation, and the other patient had improved from functional class II to I. Seven patients were severely symptomatic when first evaluated; 4 of these underwent operation for relief of outflow obstruction (3 with mitral valve replacement and 1 with ventricular septal myotomy-myectomy). During the period of follow-up, 3 of the 4 operated patients had important relief or abolition of symptoms; the other patient died 3 days after mitral valve replacement. The remaining 3 study patients had persistent limiting symptoms. Hence, at the most recent evaluation, 18 of the 22 patients with longitudinal follow-up were either asymptomatic or mildly symptomatic, and only 1 patient had died.

Family history: Genetic transmission of HC to first-degree relatives[24] could be substantiated in 13 of 25 patients. Seven of these had a family member who had died from premature sudden death (<40 years of age) due to documented or suspected HC; the 6 others had at least 1 surviving relative with HC. Although there was no family history of HC in the remaining 12 patients, systematic echocardiographic studies were not performed in these pedigrees.

Morphology: Mitral valves from 3 patients who underwent mitral valve replacement were available for gross visual examination. None of the 3 valves showed evidence of leaflet scalloping or redundancy, increased anular circumference or distorted chordal anatomy, findings characteristic of patients with primary MVP.[9,10] Mitral valve tissue area and leaflet length (from anular margin to free edge) were normal in 2 patients (area <11 cm^2; length <22 mm),[25] but were increased in the other patient (area 19 cm^2; anterior leaflet length 30 mm). Mitral valve circumferences were normal in all 3 valves (i.e., <11 cm).[25] In each patient, the anterior leaflet was focally thickened by fibrous tissue in the area of systolic contact with the ventricular septum.

DISCUSSION

HC is a primary cardiac disease in which the pattern and extent of left ventricular hypertrophy and the nature of the myopathic muscle are considered to be the principal determinants of many of the pathophysiologic and clinical consequences of this condition.[1,3] However, it is the mitral valve itself that produces obstruction to left ventricular outflow by virtue of SAM into the narrowed outflow tract and midsystolic apposition with the septum.[4-6] Although alternative explanations have been proposed,[26] many investigators favor the hypothesis that SAM is largely produced by a Venturi phenomenon in which the mitral valve is pulled toward the ventricular septum by a high-velocity systolic outflow jet.[3] Several patterns of SAM may occur.[6] Most often, both mitral leaflets move in concert toward the ventricular septum[6] and the anterior leaflet makes contact with the septum because of its forward position; less often, the posterior leaflet alone produces SAM.[23]

In the present study, we describe a subset of patients with HC and a distinctive pattern of mitral valve dynamics that extend our concepts regarding the diversity of the functional abnormalities present in this disease. In our patients, the mitral valve demonstrated SAM toward the ventricular septum and prolapse into the left atrium. Shortly after the onset of systole, the distal portion of the mitral valve leaflets moved anteriorly into the outflow tract and approached or contacted the septum; the proximal mitral valve then moved abruptly cephalad, protruding into the left atrium (5 to 15 mm beyond the mitral anular plane). The marked SAM observed in these patients reflected obstruction to left ventricular outflow, as is evidenced by hemodynamically significant intraventricular pressure gradients recorded in almost 90% of the patients who underwent cardiac catheterization.

Morphologic examination of the 3 mitral valves removed at surgery showed focal thickening of the anterior mitral leaflet typical of obstructive HC,[7,8] but without the leaflet redundancy and scalloping or increased anular circumference characteristic of "floppy" mitral valve.[9,10] Two of these valves were of normal size, whereas the other was greatly enlarged, with elongation of both the anterior and posterior leaflets, typical of many patients with HC.[27] However, because our gross morphologic observations were confined to a small number of valves, we cannot be certain whether these pathologic observations were truly representative of all 25 study patients.

However, based on the information available to us, we would conclude that the combination of SAM and MVP evident in our patients with HC is probably not explained by coexistence of a primary mitral valve abnormality, such as a floppy valve. Rather, it is most likely that the unique mitral valvular motion pattern described in this study is an expression of the anatomic and spatial disproportionality between the mitral valve apparatus and the small left ventricular cavity and distorted ventricular geometry characteristic of HC.[12-14] The fact that cephalad motion of the mitral valve into the left atrium temporally preceded mitral-septal contact in each patient studied suggests that MVP was probably not a direct consequence of SAM and outflow obstruction.

Although these patients with HC and unique mitral valvular motion proved to be uncommon among our overall patient population with HC (about 2%), they nevertheless appear to represent part of the broad pathophysiologic spectrum of this disease. For example, we found evidence of genetic transmission of HC[24] in most pedigrees of the study patients, even though it was not feasible to perform systematic echocardiographic studies in all families. Furthermore, the clinical course and demographic features, cardiac dimensions and distribution of left ventricular hypertrophy in our patients did not appear to differ substantially from other patients within the disease spectrum of HC who did not have this particular pattern of mitral valvular motion.

It should be emphasized, however, that the present study was not designed to address the question of the prevalence of MVP in patients with HC. Indeed, the frequency with which MVP occurs in HC is largely unknown. Chandraratna et al[28] reported a 10% incidence of asymmetric septal hypertrophy in a population of patients with MVP. However, that study was limited to M-mode echocardiography, the magnitude of left ventricular wall thicknesses was relatively mild, and it is uncertain whether all patients with asymmetric septal hypertrophy had HC. Also, it should be emphasized that the detection of MVP by M-mode echocardiography alone in patients with obstructive HC is difficult (if not impossible), because SAM and systolic posterior MVP occur during the same phase of the cardiac cycle.

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Comparison of Left Ventricular Ejection Fraction by Magnetic Resonance Imaging and Radionuclide Ventriculography in Idiopathic Dilated Cardiomyopathy

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To assess the validity of gated magnetic resonance imaging (MRI) in determining left ventricular (LV) ejection fraction (EF), MRI (Spin Echo, multislice-multiphase technique on the short-axis plane) was compared with equilibrium radionuclide ventriculography in 32 patients with idiopathic dilated cardiomyopathy. All patients underwent MRI and radionuclide ventriculography, performed consecutively on the same day (mean time interval between the 2 examinations: 40 minutes). Comparison with LVEF showed a high correlation ($y = 0.79 \times +3.51$, $r = 0.91$; $p < 0.001$). Mean difference between radionuclide ventriculography and MRI data was 1.7, with the 95% confidence interval 0.71 to 2.68: MRI slightly underestimated LVEF. MRI interobserver and intrapatient variability (assessed in 15 of 32 patients) showed a high correlation ($r = 0.91$, $r = 0.98$). In conclusion, data suggest that MRI, using the short-axis approach and the multislice-multiphase technique, is an accurate, noninvasive, highly reproducible method of evaluating LVEF in patients with idiopathic dilated cardiomyopathy.

(Am J Cardiol 1991;67:411–415)

Since Dodge and Sandler[1,2] validated angiographic methods for studying cardiac function, left ventricular (LV) ejection fraction (EF) has become the most frequently used clinical parameter in the diagnostic and prognostic evaluation of patients with cardiac disease.[3-5] Several noninvasive techniques have been used for assessing cardiac function. Two-dimensional echocardiography[6-8] and equilibrium radionuclide ventriculography[9-12] are the current methods used in noninvasive evaluation of LVEF. The application of gated magnetic resonance imaging (MRI) to the cardiovascular system has offered a new noninvasive modality that allows the 3-dimensional reconstruction of LV volume in any phase of the cardiac cycle.[13-17] The present study assesses the validity of MRI, compared with equilibrium radionuclide ventriculography, in determining LVEF in patients with idiopathic dilated cardiomyopathy.

METHODS

Patients: Thirty-two patients (23 men and 9 women, mean age 49 years, range 27 to 68), with clinical and echocardiographic diagnosis of idiopathic dilated cardiomyopathy, in New York Heart Association class III to IV, were studied prospectively. Exclusion criteria were atrial fibrillation or high incidence of arrhythmias, implanted pacemaker or other ferromagnetic devices (e.g., aneurysm clips), and claustrophobia. Four patients were excluded because of atrial fibrillation, and 3 because of a high incidence of ventricular arrhythmias. After giving informed consent, all patients underwent MRI and equilibrium radionuclide ventriculography, consecutively performed in our center on the same day, in the afternoon, with a time interval between the 2 examinations of 20 to 70 minutes (mean 40). There were no significant changes in heart rate and blood pressure in the interval between examinations. All patients were receiving a daily regimen of either digitalis, diuretics and nitrates, or a combination, taken in tabular form in the morning.

Magnetic resonance imaging technique: Electrocardiogram-gated MRI was performed by using a Philips Gyroscan S15 Superconducting System operating at 1.5 Tesla. All patients were imaged in the supine position using 2 different acquisition techniques, sequentially applied:

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1. Three different spin-echo imaging sequences were acquired to visualize the cardiac planes. First, a gated spin-echo multislice sequence on the transverse tomographic plane was obtained. The time echo was 30 ms; the repetition time was 80 to 90% RR; each scan was performed by using 2 measurements with reconstruction matrix 256 × 256 and a slice 10-mm thick. Then, a −25°/−30° left-right angulation was added to the image with optimal cardiac visualization to obtain an angulated transverse plane, called "four-chamber" MRI view. From this section, in which septa are perfectly aligned, an additional localizing multislice scan was performed (perpendicular to the ventricular septum) to visualize the short-axis plane (Figure 1).

The mean duration of this first part of the examination was of 15 minutes (range 12 to 19; standard deviation ±1.36).

2. A spin-echo multislice-multiphase sequence on the short-axis plane was acquired as the second part of the MRI examination. There was no interval of time between the 2 parts. This technique was used to acquire multiple contiguous slices, which cover the left ventricle from the apex to the base, in the different phases of the cardiac cycle to obtain a real 3-dimensional reconstruction of the heart and to evaluate cardiac volumes and EF. For each slice, end-diastolic and end-systolic contours were manually drawn on the computer screen. LV volume and LVEF values were automatically calculated by the computer (volume EF program) (Figures 2 and 3). MRI variables were: time echo = 30 ms; repetition time = 80 to 90% RR; 2 measurements; reconstruction matrix = 256 × 256; slice thickness = 10 mm; and number of slices or phases = 5 to 8. Mean duration of this second part of the examination was 30 minutes (range 25 to 36; standard deviation ± 1.67).

Radionuclide ventriculography technique: Equilibrium radionuclide ventriculography was performed after in vivo erythrocyte labeling with 15 mCi of technetium-99m sodium pertechnetate. Data collection was obtained with a standard single-crystal gamma camera

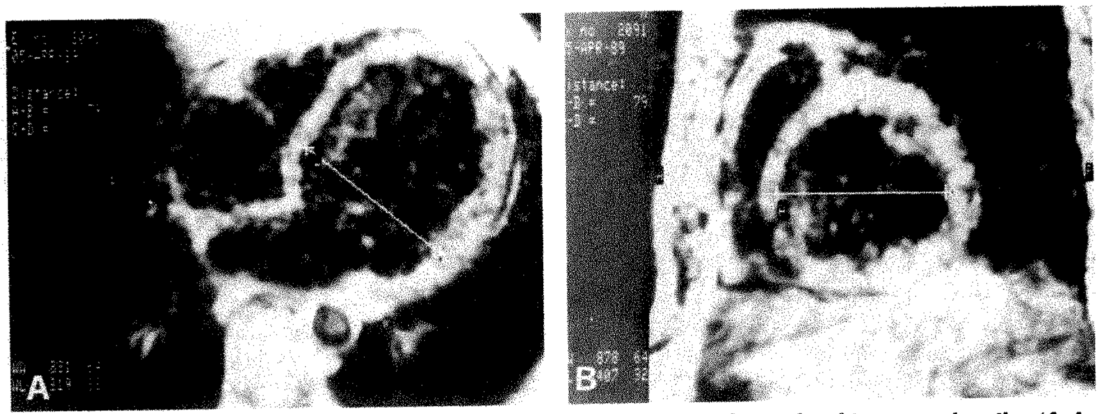

FIGURE 1. Magnetic resonance imaging visualization of oblique cardiac planes. *A*, angulated transversal section (4-chamber view), with optimal alignment of ventricular and atrial septa. *B*, imaging plane through the short axis of the left ventricle, perpendicular to the ventricular septum.

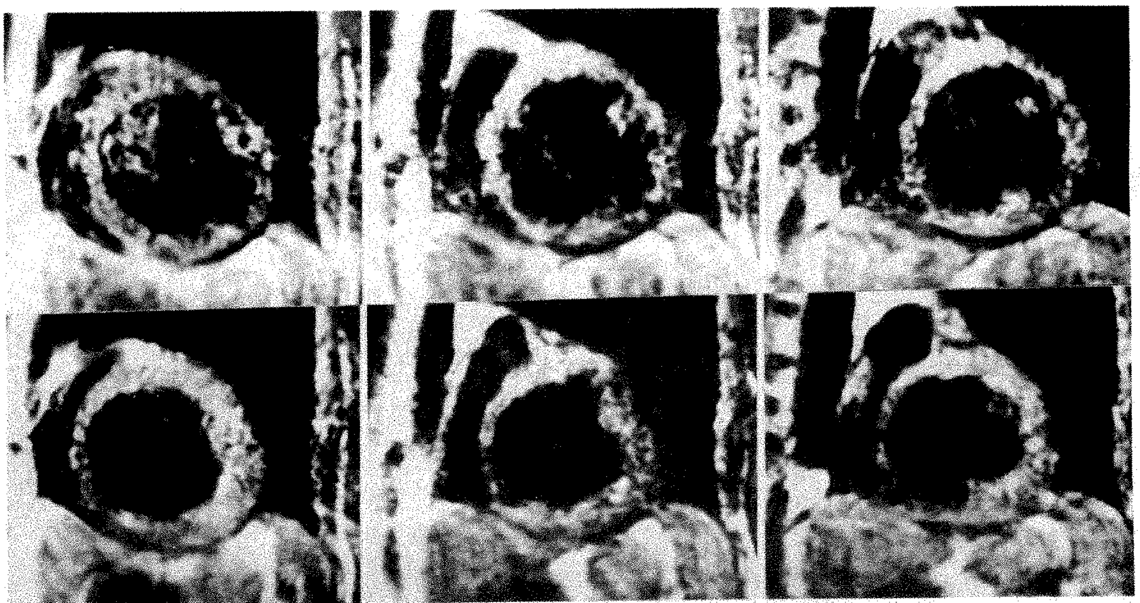

FIGURE 2. Determination of left ventricular volumes by spin-echo multislice-multiphase technique. *Upper panel*, 3 different contiguous short-axis sections from the apex to the base of left ventricle at diastole; *lower panel*, same views at systole.

(Philips Gamma Diagnostic Tomo), equipped with a low-energy, general purpose parallel-hole collimator and interfaced with a dedicated on-line computer system. Twenty-four frames per cardiac cycle were acquired in the left anterior oblique projection with an additional 10° caudal tilt. Acquisition was continued for 300 cardiac cycles. Mean duration of the whole examination was of 28 minutes (range 26 to 31; standard deviation ± 1.66). LVEF was calculated from counts within a LV region of interest, after manual functional background subtraction.

Statistical analysis: LVEF values obtained in each patient by the 2 methods were used to compare MRI and radionuclide ventriculographic results. The linear correlation coefficient between the 2 methods and linear regression analysis were calculated according to the standard approach. Agreement between the data obtained by means of the 2 techniques was assessed by the methods described by Bland and Altman.[18] Individual differences between LVEF values, estimated by means of the 2 techniques, were plotted on a graph against the mean values of the 2 measurements. The mean of the differences, together with the corresponding 95% confidence interval, was also calculated. Furthermore, linear regression analysis and the methods of Bland and Altman were also used to define interobserver and intrapatient variability to analyze the MRI examination repeatability. A p value <0.001 was considered statistically significant.

RESULTS

Table I lists LVEF values in the 32 patients. The linear correlation coefficient between the LVEF values determined by using the 2 techniques was very high: $r = 0.91$ ($p < 0.001$). The linear regression equation of LVEF values determined by using MRI on the corresponding values obtained with radionuclide ventriculography showed an intercept value of 0.79 and a slope value of +3.51 (Figure 4). Figure 5 shows the differences between LVEF measurements against the mean of the measurements by the 2 methods. The mean difference was 1.7, indicating that MRI values were slightly underestimated. The standard error of estimates was 0.50. The 95% confidence interval for the bias was 0.71 to 2.68. Thus, MRI tends to give a lower value between 0.71 and 2.68.

TABLE I Left Ventricular Ejection Fraction Data

	LVEF (%)	
Pt. No.	Radionuclide Ventriculography	MRI
1	30	28
2	33	26
3	26	24
4	27	27
5	21	18
6	20	19
7	19	20
8	21	20
9	17	17
10	18	19
11	27	22
12	28	23
13	20	17
14	22	18
15	30	25
16	30	28
17	28	25
18	25	25
19	29	30
20	33	28
21	27	28
22	28	28
23	18	18
24	20	18
25	24	22
26	23	22
27	26	26
28	29	26
29	18	19
30	19	21
31	31	27
32	40	38
Mean ± SD	25 ± 5.5	23 ± 4.8

LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; SD = standard deviation.

Magnetic resonance imaging interobserver and intrapatient variability: Interobserver variability of MRI examination, assessed in 15 of 32 patients (chosen at random) by 2 investigators, who independently interpreted the same study a week apart, was small for

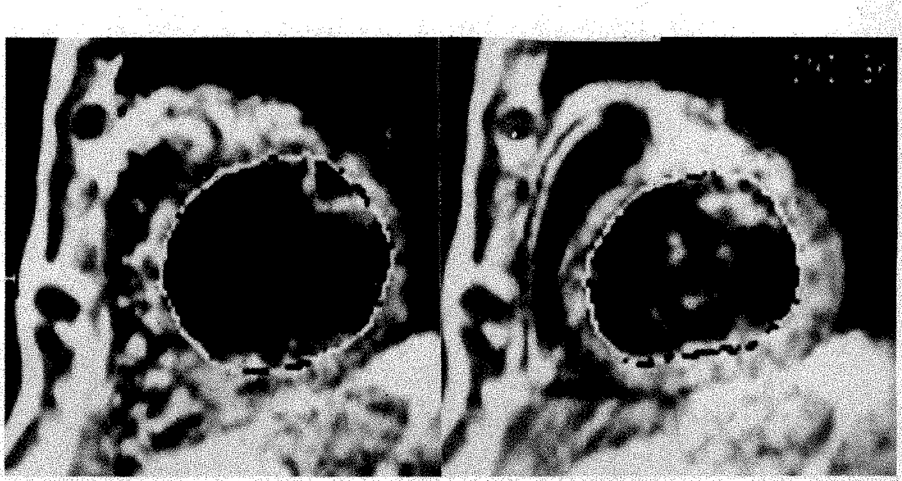

FIGURE 3. Left ventricular ejection fraction, automatically calculated by the computer, and obtained by magnetic resonance imaging multiple contiguous slices.

LVEF measurements. The following parameters indicating interobserver variability were: r = 0.91, mean difference = 0.4, standard deviation = 1.13, and standard error of estimates = 0.29. Intrapatient variability was evaluated by 1 of the investigators in 15 of 32 patients (chosen at random), by repeating MRI examination 24 hours later, after which there were no significant changes in heart rate and blood pressure. We also performed blind measurements at least 1 month after the first interpretation. The correlation between data was very high. The following parameters indicating intrapatient variability were: r = 0.98, mean difference = 0.36, standard deviation = 0.75, and standard error of estimate = 0.19.

DISCUSSION

To validate LVEF measurements in patients with idiopathic dilated cardiomyopathy, MRI was compared with equilibrium radionuclide ventriculography, mainly because this technique is also relatively noninvasive and it does not rely on geometric assumption for LVEF calculation. On the other hand, it was critical for us to perform the 2 examinations consecutively on the same day, thus minimizing the hemodynamic changes of the patients. The assessment of LV geometry and function by MRI has been considered more accurate in the short-axis than in the transverse or long-axis plane, because angulation errors and partial volume effects could be minimized.[19-21] The present study used a spin-echo multislice-multiphase sequence on the short-axis plane. This method allows acquisition of multiple contiguous slices, which cover the left ventricle from the apex to the base, in the different phases of the cardiac cycle, with an optimal visualization of LV wall and a very high definition of the endocardium. Furthermore, by this technique, the LV volumes and LVEF are automatically calculated (volume EF program), without using any geometric assumption. A similar imaging strategy was used by Van Rossum et al,[22] who compared MRI with LV angiography (performed on different days) in patients with various cardiac diseases, and obtained a high correlation. This MRI method of calculating LVEF by 3-dimensional reconstruction of the real LV volumes has showed a very high correlation with radionuclide ventriculographic data. The mean difference between radionuclide ventriculography and MRI values was 1.7,

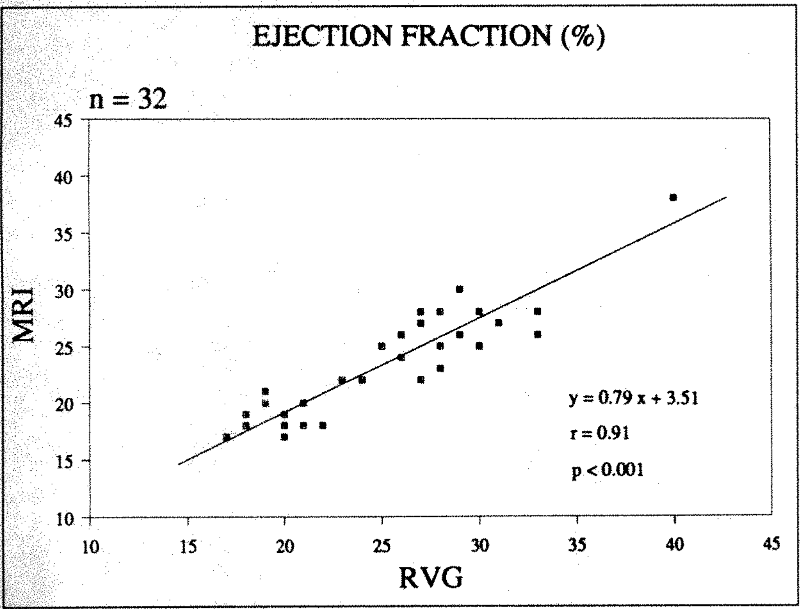

FIGURE 4. Correlation between left ventricular ejection fraction obtained by magnetic resonance imaging (MRI) and equilibrium radionuclide ventriculography (RVG).

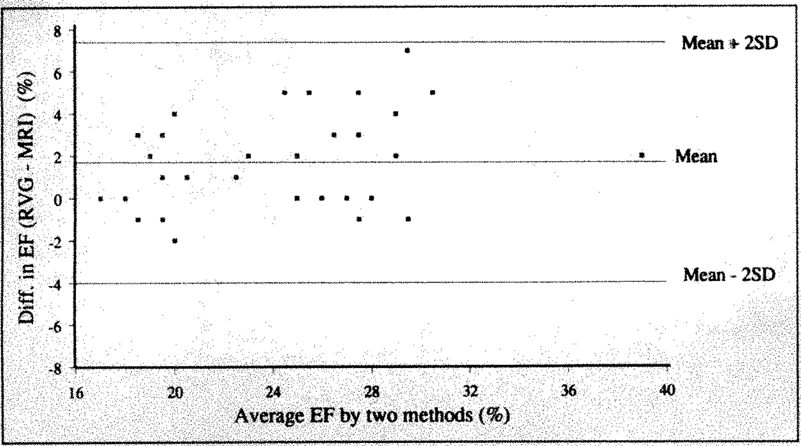

FIGURE 5. Differences (Diff.) between left ventricular ejection fraction (EF) against the mean of measurements by 2 methods. MRI = magnetic resonance imaging; RVG = radionuclide ventriculography; SD = standard deviation.

with a 95% confidence interval of 0.71 to 2.68; this indicates that MRI slightly underestimates LVEF. Despite this finding, the standard deviation of differences was 2.85, small enough for us to be confident that the 2 methods can be used interchangeably.

Repeatability of magnetic resonance imaging: The study of variability was performed to assess the accuracy of LV edge detection (interobserver variability) and the MRI examination repeatability (intrapatient variability). The high correlation between measurements of 2 observers (r = 0.91) reflects the low degree of variability inherent in deriving measurements from the images. We have also obtained a high correlation (r = 0.98) in LVEF determination on 2 occasions separated by an interval of 24 hours (intrapatient variability), thus reflecting the optimal reproducibility of MRI examination. In fact, compared with other imaging techniques, such as echocardiography, by which 1 cross-sectional level among separated studies of the same patient cannot be exactly reproduced, MRI examination, in which parameters are completely computerized and totally independent from the operator, can be exactly reproduced on the same section levels. The small interobserver and intrapatient variability indicates that MRI may be an ideal method for evaluating and following up patients with idiopathic dilated cardiomyopathy and can be used for assessing response to therapeutic interventions.

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Stroke Volume During Submaximal Exercise in Endurance-Trained Normotensive Subjects and in Untrained Hypertensive Subjects with Beta Blockade (Propranolol and Pindolol)

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The effect of β-adrenergic blockade on stroke volume (SV) at increasing submaximal exercise intensities was studied in 12 endurance-trained normotensive and 12 untrained hypertensive (diastolic blood pressure >95 mm Hg) men, aged 18 to 34 years. Subjects were assigned to each of 3 treatments in a double-blind, randomized order: placebo, propranolol (80 mg twice daily) and pindolol (10 mg twice daily) for 10 days, with a period of 48 to 60 hours from the initial dose to the first treadmill test and a 4-day washout period between drugs. Cardiac output was measured using the carbon dioxide rebreathing method and SV was calculated from cardiac output and heart rate as follows: SV = cardiac output/heart rate. Cardiac outputs were estimated at rest and while walking on a treadmill at 25, 45, 60 and 75% of the subject's previously determined maximal oxygen uptake ($\dot{V}O_2$max). No significant differences were found in cardiac output between either of the drugs and placebo at rest, or at any of the 4 rates of work. Propranolol significantly increased SV above placebo values ($p <0.05$) for both trained and untrained groups at the intensities of 45, 60 and 75%. Significant differences in SV were found between pindolol and placebo only at the intensities of 60 and 75% in the trained group. Contrary to expectations, SV showed no indication of a plateau with propranolol in the trained subjects throughout the 4 different exercise intensities, whereas a plateau was established under placebo conditions by 45% of $\dot{V}O_2$max in both trained and untrained subjects. These results suggest that both trained and untrained hypertensive persons can exercise with β-adrenergic blockade at submaximal levels without compromised cardiac function.

(Am J Cardiol 1991;67:416–421)

Widespread use of β-adrenergic blockade as a treatment for hypertension,[1,2] ischemic heart disease and postmyocardial infarction[3,4] has raised many questions concerning the effect of these drugs during exercise. Since exercise is often prescribed as an adjunct treatment in combination with β blockade,[1,5-7] the patient's ability to maintain satisfactory cardiac function during exercise, as well as at rest, is important.

Differing properties of β blockers may, or may not, be present in any 1 specific drug. Several of these properties can have a major impact on a person's response to both acute and chronic activity.[8] As an example, the property of β_1 selectivity, or cardioselectivity, has been shown to provide substantial benefit during both acute bouts of exercise and exercise training[8-10] compared with nonselective drugs. Intrinsic sympathomimetic activity (ISA) is another property that may provide significant benefit during exercise, since ISA does allow some sympathetic stimulation of β adrenoreceptors. One study[11] showed that pindolol, a β blocker with ISA, allows for a higher submaximal exercise cardiac output and submaximal double product than does propranolol. Thus, drugs with this ISA property could possibly attenuate the decreases in cardiac output and heart rate that have been reported to occur both at rest and during exercise with non-ISA drugs.[3,4,8-10,12-16] In studies in which β blockers with ISA have been used, the normal decline in heart rate with β blockade is significantly attenuated at rest and during low-intensity exercise.[13,15,16]

The present study examined cardiac output, stroke volume (SV) and heart rate at varying submaximal exercise intensities in both untrained hypertensive and endurance-trained normotensive men to ascertain if drugs with ISA properties are better able to maintain cardiac function both at rest and during exercise. Portions of the hypertensive subjects' data from this study have been published previously.[17]

METHODS

Twenty-four men, aged 18 to 34 years, were recruited from students and staff at The University of Texas at Austin, and from members of the greater Austin community. The subjects were classified into 2 groups: 12 untrained hypertensives and 12 endurance-trained [maximum oxygen consumption ($\dot{V}O_2$max) >53

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ml·kg^{-1}·min^{-1}] normotensives. These 2 subject groups were chosen to represent (1) a population that would most likely be prescribed this medication, and (2) a population that would exhibit the greatest attenuation in exercise capacity in response to β-adrenergic blockade.[9] Ideally, endurance-trained hypertensive subjects would have been used, but an adequate subject pool was not available.

Untrained subjects who were taking hypertensive medication to control blood pressure, stopped taking this medication for a period of 2 weeks before starting this study. These subjects had to demonstrate an unmedicated diastolic blood pressure >95 mm Hg on 3 consecutive days. Each subject received a physical examination that included a resting and exercise electrocardiogram. The protocol was approved by the University of Texas at Austin Institutional Review Board and all subjects provided written informed consent. Subject characteristics are listed in Table I.

Subjects were given each of 3 treatments: placebo, pindolol (10 mg twice daily) and propranolol (80 mg twice daily) in a randomized, double-blind manner. Drugs were self-administered orally, and subjects began medication no less than 48 hours before the first test. Subjects continued to take the medication for a minimum of 10 days and were instructed to take medication 90 minutes to 2 hours before each testing session. Medication periods were followed by a washout period of 4 days before beginning the next medication period. Additional submaximal tests, to be reported elsewhere, were conducted on those days following the test day reported in this paper, necessitating 10-day medication periods.

The initial testing session, before starting medication, was used to determine the subject's $\dot{V}O_2$max. A SensorMedics Horizon metabolic measurement cart was used for determining expired ventilation, $\dot{V}O_2$, carbon dioxide production and respiratory exchange ratio.[18] The subjects walked on a treadmill with gradually increasing speed and grade, until the subject could no longer continue. The exercise test protocol has been described previously.[10] The peak $\dot{V}O_2$ achieved was assumed to be $\dot{V}O_2$max, having met the requirements of a respiratory exchange ratio ≥1.15 and a maximum heart rate within the expected range. A diagnostic 12-lead electrocardiogram was recorded during this testing session and no abnormalities were identified for any of the test subjects. From this initial test, the $\dot{V}O_2$ values at 25, 45, 60 and 75% of directly measured $\dot{V}O_2$max were calculated. Treadmill speeds and grades required to elicit the values representative of these percentages of $\dot{V}O_2$max were calculated for use in each of the remaining tests.

The subsequent tests, which began no less than 48 hours after beginning each medication period, involved estimating cardiac output at rest, 25, 45, 60 and 75% of $\dot{V}O_2$max using the carbon dioxide rebreathing technique.[19] After completing the last submaximal work rate (75%), the test was continued until the subject reached exhaustion. A total of 2 rebreathing trials were performed during 8-minute periods at rest and at each exercise intensity, and the average of the 2 trials was used for all subsequent analysis. Heart rates were measured with a 3-lead electrocardiogram and SV was calculated as SV = cardiac output/heart rate. This protocol was repeated during each drug treatment period.

TABLE I Physical Characteristics (mean ± standard deviation) of the Subjects in the Trained and Untrained Hypertensive Groups

	Groups	
	Trained	Untrained Hypertensive
n	12	12
Age (years)	24 ± 0.7	23 ± 0.9
Height (cm)	174 ± 1.8	175 ± 1.5
Weight (kg)	70 ± 2.0	89 ± 2.7*
$\dot{V}O_2$max (ml · kg^{-1} · min^{-1})	58 ± 1.7	40 ± 1.9*

* Significant ($p \leq 0.05$).

A 2 × 3 × 5 ("training" × "drug" × "rate of work") analysis of variance, with repeated measures design, was used to determine overall main effects. The repeated measures were "drug" and "rate of work." Data were analyzed with the Biomedical Statistics Package 2V (BMDP 2V). Post hoc comparisons were made using Tukeys Honestly Significant Difference test. All tests were conducted using a $p < 0.05$ significance level.

RESULTS

There were significant ($p < 0.05$) main effects for level of training ($\dot{V}O_2$max, trained versus untrained), drug and rate of work (Table II). Because of intentional differences in the characteristics between the trained normotensive and untrained hypertensive subjects on the basis of their selection into groups, no attempts were made to compare the 2. Comparisons will be made between the effects of drug and rate of work for each group independently.

In the untrained hypertensive group, heart rates were significantly lower with both drugs compared with placebo at all rates of work except for pindolol at 25% of $\dot{V}O_2$max. The greatest magnitude of heart rate reduction at rest and during exercise was found with propranolol, with pindolol eliciting heart rates between propranolol and placebo values (Figure 1A). With propranolol, SV increased significantly above placebo values at 45 through 75% of $\dot{V}O_2$max. With pindolol, SV was not significantly different from placebo, but it was significantly lower compared with propranolol conditions (Figure 1B). SV plateaued by 45% of $\dot{V}O_2$max with placebo and pindolol, but not until 60% of $\dot{V}O_2$max with propranolol. No significant differences were found in cardiac output between placebo, pindolol and propranolol conditions, at rest or during submaximal exercise at any of the 4 intensities (Figure 1C).

In the trained group, although only propranolol was significantly different from placebo at rest, both drugs produced heart rates significantly lower than placebo, from 25 through 75% of $\dot{V}O_2$max, again with propranolol producing the greatest magnitude of reduction (Figure 2A). Pindolol resulted in SV not significantly different from placebo, whereas propranolol resulted in SV significantly higher than placebo at rest, and 45, 60 and 75% of $\dot{V}O_2$max. Further, SV was significantly lower with pindolol compared to propranolol conditions at 60 and 75% of $\dot{V}O_2$max. In addition, the presence of a plateau in SV was not demonstrated with propranolol from rest through 75% of $\dot{V}O_2$max (Figure 2B), whereas the expected plateau was clearly seen with placebo and pindolol at 45 and 60% of $\dot{V}O_2$max, respectively, and with all 3 treatments in the untrained hypertensive group. Cardiac output values were not significantly different from placebo under the 2 drug conditions at rest and during exercise, although with both drugs there was a trend for cardiac output to be slightly lower than placebo (Figure 2C).

DISCUSSION

The data from this study suggest that both endurance-trained normotensive and untrained hypertensive subjects receiving β blockade with propranolol and pindolol are able to maintain cardiac output at rest and during exercise through 75% of $\dot{V}O_2$max. This occurs despite a significantly lower heart rate at all rates of work in both groups of subjects with propranolol, and at 25 to 75% in the trained group and at 45 to 75% of $\dot{V}O_2$max in the untrained hypertensive group with pindolol. Changes in SV, and the factors contributing to these changes, are primarily responsible for the subject's ability to maintain cardiac output in the presence of an attenuated heart rate.

The differences in cardiovascular adaptations to exercise between propranolol and pindolol were quite

TABLE II Cardiac Output, Stroke Volume and Heart Rate Responses at Rest and During Exercise at 25, 45, 60 and 75% of Maximal Oxygen Uptake (mean ± standard error)

Variable	Rest	25%	45%	60%	75%
Untrained Subjects					
Propranolol					
Cardiac output (liters · min^{-1})	3.6 ± 0.2	8.3 ± 0.4	11.1 ± 0.5	13.6 ± 0.6	15.4 ± 0.9
Stroke volume (ml · beat^{-1})	61 ± 3	104 ± 4	120 ± 5	128 ± 5	128 ± 7
Heart Rate (beats · min^{-1})	58 ± 2	79 ± 3	93 ± 2	108 ± 2	122 ± 3
Pindolol					
Cardiac output (liters · min^{-1})	3.5 ± 0.2	8.5 ± 0.4	11.2 ± 0.5	13.0 ± 0.5	14.6 ± 0.7
Stroke volume (ml · beat^{-1})	50 ± 3	95 ± 5	109 ± 5	114 ± 5	114 ± 6
Heart rate (beats · min^{-1})	69 ± 2	91 ± 3	103 ± 2	116 ± 2	129 ± 2
Placebo					
Cardiac output (liters · min^{-1})	3.7 ± 0.2	9.0 ± 0.4	11.6 ± 0.6	13.9 ± 0.7	16.0 ± 0.9
Stroke volume (ml · beat^{-1})	48 ± 3	91 ± 6	99 ± 6	101 ± 5	97 ± 6
Heart rate (beats · min^{-1})	78 ± 3	100 ± 3	117 ± 4	139 ± 5	166 ± 4
Trained Subjects					
Propranolol					
Cardiac output (liters · min^{-1})	3.5 ± 0.2	8.7 ± 0.4	12.1 ± 0.4	15.2 ± 0.4	18.3 ± 0.7
Stroke volume (ml · beat^{-1})	75 ± 4	116 ± 3	138 ± 4	148 ± 4	157 ± 5
Heart rate (beats · min^{-1})	47 ± 2	74 ± 3	88 ± 2	103 ± 2	117 ± 3
Pindolol					
Cardiac output (liters · min^{-1})	3.6 ± 0.2	9.0 ± 0.4	12.5 ± 0.4	15.3 ± 0.5	17.7 ± 0.4
Stroke volume (ml · beat^{-1})	65 ± 3	108 ± 4	130 ± 4	139 ± 5	141 ± 4
Heart rate (beats · min^{-1})	55 ± 3	83 ± 3	96 ± 2	111 ± 3	125 ± 3
Placebo					
Cardiac output (liters · min^{-1})	4.1 ± 0.5	9.5 ± 0.4	14.0 ± 0.9	17.0 ± 0.9	18.8 ± 0.8
Stroke volume (ml · beat^{-1})	62 ± 5	103 ± 5	117 ± 6	120 ± 5	112 ± 5
Heart rate (beats · min^{-1})	65 ± 3	93 ± 3	117 ± 3	143 ± 4	168 ± 4

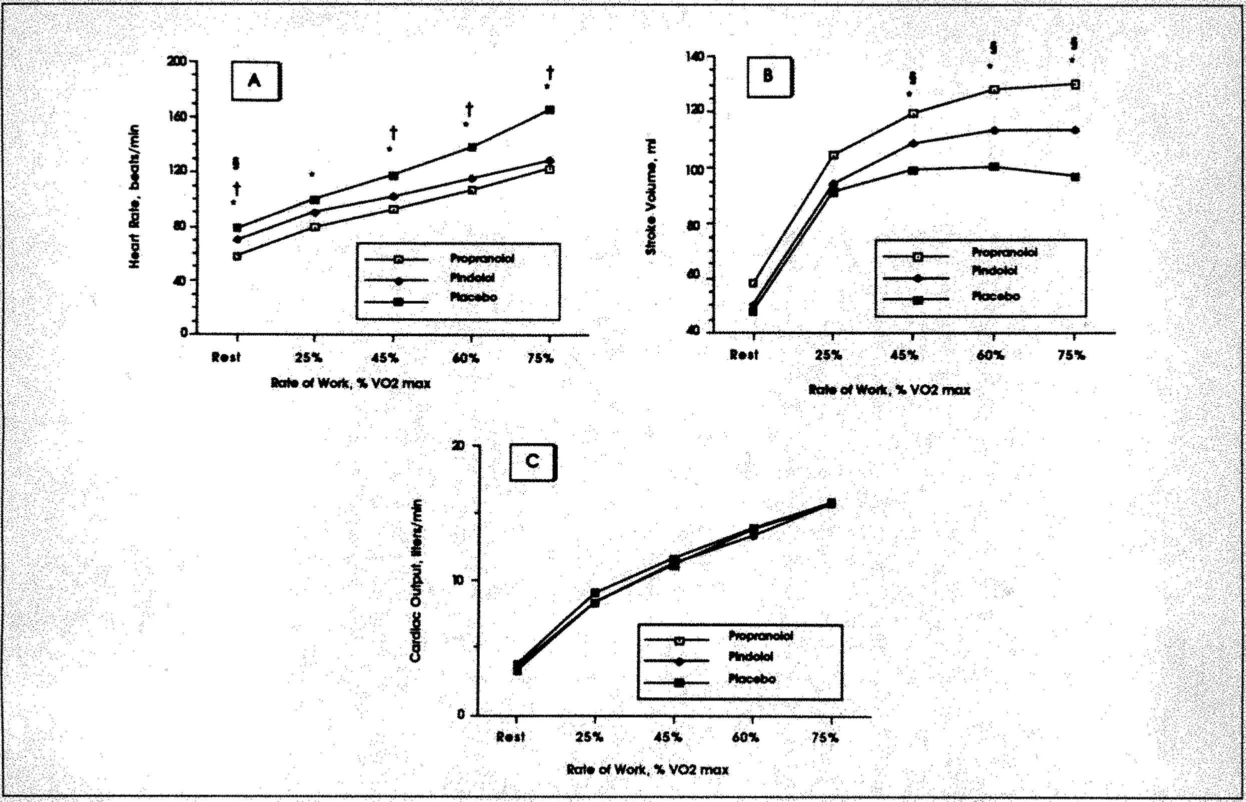

FIGURE 1. Heart rate *(A)*, stroke volume *(B)* and cardiac output *(C)* in untrained subjects at rest, and 25, 45, 60 and 75% of maximal oxygen uptake (VO_2max). † = pindolol significantly different from placebo values; § = pindolol significantly different from propranolol values; * = propranolol significantly different from placebo values.

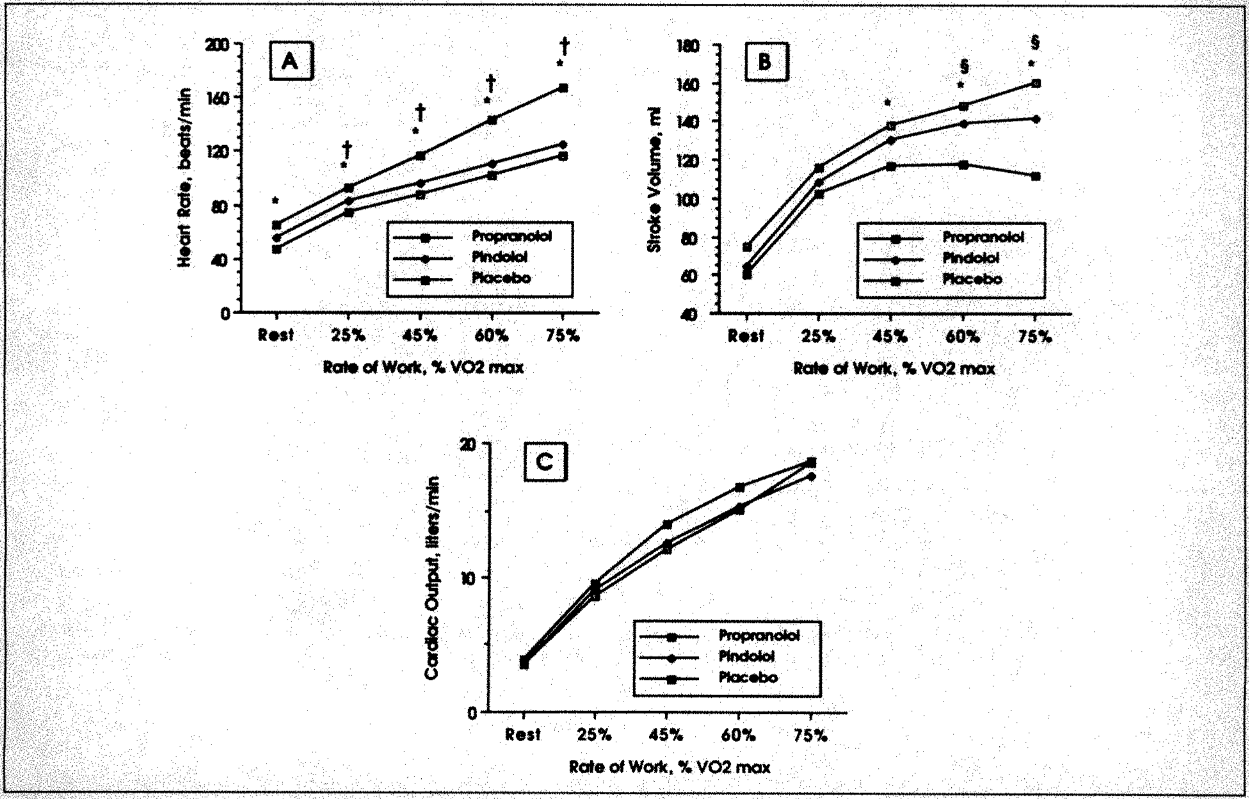

FIGURE 2. Heart rate *(A)*, stroke volume *(B)* and cardiac output *(C)* in trained subjects at rest, and 25, 45, 60 and 75% of maximal oxygen uptake (VO_2max). † = pindolol significantly different from placebo values; § = pindolol significantly different from propranolol values; * = propranolol significantly different from placebo values.

marked. Exercise with pindolol resulted in cardiac output and SV values very similar to those seen with placebo, even though heart rate was significantly reduced with pindolol in both trained and untrained hypertensive groups. The attenuation in heart rate with pindolol, however, was of lesser magnitude than that with propranolol. Propranolol, while allowing the subjects to maintain cardiac output, achieved this through significantly higher SVs and lower heart rates at most intensities in both trained and untrained groups.

The absence of a plateau in SV with propranolol in the trained group was quite unexpected. Under normal conditions, a plateau would have been expected between 40 and 60% of $\dot{V}O_2$max.[20] Bevilacqua et al[21] also reported that SV increased up through 100% of $\dot{V}O_2$max in 10 untrained healthy men while taking propranolol, but, unlike the present study, under placebo conditions it reached its peak at 25% of $\dot{V}O_2$max and then decreased slightly. Unfortunately, they did not test their subjects to maximal levels, stopping at approximately 85% of the age-predicted maximal heart rate. What they refer to as 25, 50, 75 and 100% of $\dot{V}O_2$max represent, in fact, 25, 50, 75 and 100% of the maximum heart rate attained during the test that they terminated at approximately 85% of the age-predicted maximal heart rate. The mean heart rate they reported at 100% of $\dot{V}O_2$max under placebo conditions was only 169 beats/min, a value that is 20 to 30 beats under what would be expected for a maximal heart rate for this age group. Since these were not true maximal tests, it is impossible to interpret their data.

Several theories attempt to explain the body's ability to maintain cardiac output in the presence of low heart rates by increasing SV. Higginbotham et al,[22] using right-sided cardiac catheterization, radionuclide angiography and expired gas analyses, found that during low-intensity exercise, a linear increase in cardiac index with an increasing rate of work was due to an increase in both heart rate and SV index. The increase in SV index was proposed to be the result of an increase in left ventricular filling pressure and an increase in end-diastolic volume index, i.e., the Frank-Starling response. They found, to a much smaller extent, that a decrease in the end-systolic volume index was also responsible for SV increases. They also concluded that the limiting factor for SV increases at higher rates of work is a decrease in diastolic filling time, resulting from high heart rates. This was illustrated by the fact that the greatest end-diastolic volume decreases were demonstrated in their young subjects with the highest heart rates.

However, it has also been suggested that reduced diastolic filling time may not be the sole, or even major, limiting factor to SV increases at higher intensities of exercise. Tanaka et al[23] compared the cardiac function of trained and untrained subjects during exercise, from submaximal through maximal intensities, using impedance cardiography. In contrast to Higginbotham et al,[22] their data indicate that there is adequate filling of the ventricle even at the higher heart rates. Their trained subjects exhibited significantly higher values for SV and cardiac output than the untrained subjects, even at matched heart rates. Their untrained subjects experienced a decrease in SV at heart rates above 130 beats·min^{-1}, whereas their trained subjects demonstrated a plateau, or even a slight increase, in SV from heart rates of 120 beats·min^{-1} to maximum heart rate. They hypothesized that this response in the trained subjects is due to a facilitation of left ventricular filling and an increase in systolic emptying, possibly related to a decreased peripheral vascular resistance.

Crawford et al[24] examined SV, end-diastolic volume, end-systolic volume and ejection fraction in both competitive and noncompetitive runners at rest and during upright exercise on a cycle ergometer, using 2-dimensional echocardiography. The groups were compared at rest, and at 60, 70 and 85% of maximum heart rate, and at maximum heart rate. As with the propranolol treatment in the trained group in the present study, they found SV to increase significantly in the competitive group through 70% of maximum heart rate. There was a trend for SV to continue to increase through maximal exercise, although the changes beyond 70% of maximum heart rate were not statistically significant. The increase in SV was due to an almost parallel increase in end-diastolic volume, thus illustrating the importance of the Frank-Starling mechanism, especially up to 70% of maximum heart rate. The ratio of systolic blood pressure to end-systolic volume, an index of myocardial contractility, increased significantly only >70% of maximum heart rate.

These results support the contention of Plotnick et al[25] that increases in SV are due primarily to the Frank-Starling mechanism during lower intensity exercise and to increased myocardial contractility during higher intensity exercise. Crawford et al[24] also reported that the competitive group, in addition to having a larger left ventricular size than the noncompetitive group, were also able to increase end-diastolic volume proportionally more during exercise than the noncompetitive group. Thus, it appears that the increase in end-diastolic volume in athletes is a major adaptation to endurance training and that highly trained runners make greater use of the Frank-Starling mechanism during high-intensity exercise than less well-trained runners.

Although published reports agree on the fact that increased end-diastolic volume is primarily responsible for SV increases during exercise, particularly at the lower intensities of exercise, the underlying cause of this occurrence remains unclear. The data from the present study support the data of Higginbotham et al[22] who propose an increased diastolic filling time as a major factor in SV increase. However, other possible causes, such as an increased end-diastolic volume due to an increased filling pressure, cannot be overlooked, particularly when subjects are taking β-adrenergic blockade.[21] The trained and untrained groups in the present study did not demonstrate the same response during the propranolol treatments. Although SV continued to increase in the trained group, SV in the untrained hypertensive group did reach a plateau. Filling pressure may well be higher in the trained group.

Acknowledgment: Many people have contributed to the completion of this study. We would like to acknowledge the assistance of all of those subjects who participated in this study. A special thanks to Stephen Silverman, PhD, and Andrew Bullen who provided guidance in the statistical analysis and interpretation of the data. Finally, we would like to thank Sandoz Pharmaceuticals who made this study possible through a support grant from Sandoz Research Institute, East Hanover, New Jersey.

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Therapeutic Cardiac Ultrasound

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and Eric C. Everbach, PhD

Most physicians consider ultrasound as purely diagnostic, free of significant biologic effects. This paradigm is incorrect (there are significant bioeffects[1,2]) and may limit potentially beneficial therapy. The purpose of this editorial is to review 6 areas of potentially therapeutic cardiologic application of ultrasound: (1) ultrasound valvuloplasty, (2) ultrasound angioplasty, (3) the "acoustic filter" for cardiopulmonary bypass, (4) increasing cardiac inotropy with ultrasound, (5) ultrasonic pacing and defibrillation, and (6) control of drug release by external ultrasound application.

Many of these effects are due to "acoustic cavitation," the term used to describe the rapid growth and sudden implosion of a small bubble in a sound field, which yields intense, very localized heat and delivers a shock to nearby surfaces. Cavitation may also lead to local free radical production and even electromagnetic radiation in the visible spectrum ("sonoluminescence"). Direct heating by ultrasound and cavitation are the most important mechanisms of ultrasound bioeffects.

ULTRASOUND VALVULOPLASTY

Lithotripsy catheters may be useful for valve decalcification during cardiac surgery.

In 1988, Worley et al[3] reported that the intraoperative decalcification of stenotic aortic valves could be aided by a hand-held lithotripsy system. They used a commercially available electrohydraulic catheter to deliver acoustic shocks to calcific deposits on aortic valves submersed in saline at autopsy or during surgery. They believed that the procedure aided operative aortic valve repair, although they warned that the technique had the potential to cause aortic valve damage. Only mild aortic insufficiency was noted at the completion of the procedure in the initial 5 patients.

Since then, several groups have studied various high-intensity ultrasound techniques.[4-6] In another study, 10 patients with calcific aortic stenosis were treated by intraoperative aortic valve calcium debridement using the Cavitron® Ultrasonic Surgical Aspirator.[7] All had significant improvement in aortic valve area and gradient at repeat cardiac catheterization. However, half of the patients had a 1-grade worsening of their aortic insufficiency at follow-up catheterization compared to preoperative aortography. The investigators concluded that "worsening aortic insufficiency is a frequent result and will likely limit widespread application" of the technique.[7] Another interpretation of these data is that surgeons may have a significant learning curve or that further instrument development will be necessary, or both. Therefore, it is unclear what role high-intensity sound will play in cardiac operations.

ULTRASOUND ANGIOPLASTY AND THROMBOLYSIS

High-intensity ultrasound may ablate atherosclerotic tissue and, via catheter delivery systems, effect recanalization of obstructed or occluded vessels.

Angioplasty: It has been known for more than a decade that high-intensity sound can cause tissue damage and destruction ("ablation").[8] Ultrasonic ablation of atherosclerotic plaque with the goal of "ultrasonic angioplasty" was first reported and subsequently developed by Siegel et al.[9-11] Complete atherosclerotic occlusions have been recanalized in autopsy material[9] and in an animal model,[10] and initial clinical experience includes successful recanalization of 4 total occlusions and 4 high-grade stenoses in femoral or popliteal arteries.[11] Other investigators involved in ultrasound angioplasty include Freeman,[12] Marraccini,[13] Rosenschein,[14,15] Ernst[16,17] (in our laboratory) and their co-workers. Rosenschein's system has also been used in initial clinical trials in patients with peripheral vascular disease, with successful recanalization of 7 totally occluded arteries in 6 patients.[15]

Thrombolysis: High-intensity ultrasound can ablate organic material, probably via a mechanism involving acoustic cavitation. Thus, it would be expected that high-intensity ultrasound can destroy thrombi. This has in fact been reported in vitro.[18,19]

ACOUSTIC FILTER

Traveling acoustic waves can remove harmful microbubbles from cardiopulmonary bypass machines that are not removed by current mechanical filter technology.

Postcardiopulmonary bypass encephalopathy ("pump head"): A frequent neurologic complication of surgery involving cardiopulmonary bypass is a subtle encephalopathy, manifested as memory loss, personality changes, difficulty in concentrating, intellectual func-

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tioning, and so forth.[20] We call this encephalopathy "pump head." Although the etiology of pump head is probably multifactorial, the most important factor may be microembolization of the brain, with microbubbles of a diameter between 8 (large enough to block cerebral capillaries) and 35 to 40 μm (the pore size of the mechanical filters used on cardiopulmonary equipment). Other factors include microembolization with particulate material and altered cerebral perfusion.

We have developed a nonmechanical acoustic filter that can remove microbubbles of <35 μm in diameter from cardiopulmonary bypass lines without causing significant hemolysis or increased resistance.[21] The acoustic filter uses low-frequency, high-intensity ultrasound to sweep microbubbles from flowing blood with acoustic radiation force ("acoustic wind"). This device holds promise for preventing pump head.

CONTINUOUS-WAVE ULTRASOUND

Continuous-wave ultrasound can increase the force of cardiac muscle contraction in isolated rat papillary muscle.

Cardiac inotropy: In 1985 Forester et al[22] reported that isolated rat papillary muscles could be stimulated to contract more vigorously by continuous-wave ultrasound. They used low-frequency ultrasound (963 kHz) at intensities of 0.25, 0.5, 1.0 and 2.0 W/cm^2. Data revealed a significant increase in peak developed force, peak rate of force development, and peak rate of myocardial relaxation, which was linearly related to ultrasound intensity. The mechanism of this phenomenon was not related to heating alone.

Zakharov et al[23] challenged the inotropic effect of low-frequency ultrasound on isolated rat papillary muscle. They used 543 kHz ultrasound with intensities of up to 3 W/cm^2. This was found to be associated with reversible membrane depolarization and loss of membrane excitability. The mechanism of ultrasound action was thought to be related to cavitation. How cavitation alters contraction on a subcellular and molecular level remains undetermined and is a promising field for further investigation.

ULTRASONIC PACING AND DEFIBRILLATION

High-intensity ultrasound has been used for cardiac pacing and defibrillation in animal studies.

Defibrillation: Smailys et al[24] reported in 1981 that continuous-wave ultrasound at a frequency of 500 kHz and an intensity of 10 W/cm^2 could occasionally reverse ventricular fibrillation in dogs. Studies of this dose of ultrasound in the isolated right ventricles of rabbits suggested that the antiarrhythmic action of the ultrasound was related to prolonging the refractory period of the myocardial cells.

Cardiac pacing: It is known that mechanical stimulation of the heart can result in premature contractions. It might thus be expected that acoustic shock waves above a certain threshold could also induce ventricular contraction, because they are mechanical. Acoustic shock waves from lithotriptors have long been known to induce premature ventricular contractions: To avoid premature contractions, lithotriptor shocks are electrocardiographically gated. Thresholds for inducing cardiac contraction by lithotripsy shocks are under investigation (personal communication, Diane Dalecki, Medtronics Fellow, Rochester Center for Biomedical Ultrasound, University of Rochester, New York). It has also recently been noted that cardiac pacing can be achieved with the acoustic shock waves that result from laser pulses used for laser angioplasty.[25]

EXTERNAL ULTRASOUND

Controlled release of stored subcutaneous drug deposits can be achieved by external ultrasound.

Enhanced drug release from implants: Kost et al[26] recently reported that the rate of release of tracer molecules from subcutaneous implants in rats could be increased 10- to 20-fold by the external application of ultrasound to the implants. The release rate increased in proportion to the intensity of the ultrasound. Temperature and mixing were not the mechanisms of acceleration of release, which was thought by the investigators to be related to cavitation. They concluded that "with further study, ultrasound may prove useful as a way of externally regulating release rates from polymers in a variety of situations where on-demand release is required."

CONCLUSION

Ultrasound is usually considered a purely diagnostic tool in cardiology. However, there are many therapeutic applications being developed in basic acoustics and in animal physiologic laboratories, and some of these may achieve clinical usefulness in the coming decade.

Acknowledgment: We would like to thank Edwin L. Carstensen, PhD, for manuscript review and helpful suggestions, and Pat Faiello for secretarial assistance.

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Relation Between Late Potentials and Echocardiographically Determined Left Ventricular Mass in Healthy Subjects

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High-frequency, low-amplitude signals, also known as ventricular late potentials, can be recorded in patients affected with myocardial infarction in the terminal portion of the QRS complex and ST segment.[1] The slow and inhomogeneous activation of the infarcted area represents the substrate of electrical signals that can be recorded beyond ventricular activation.[2] The prolonged QRS duration may reflect this abnormal activation, but one can speculate, as did Gomes et al,[1] that a longer QRS duration may be the expression of a greater mass of myocardium that is depolarized. We recently found in healthy subjects a positive linear correlation between signal-averaged QRS duration and body size.[3] Based on the aforementioned assumptions, we hypothesized that in healthy subjects ventricular late potentials could be related to ventricular mass. This study examines the relation between the filtered QRS duration, the duration of the terminal portion of the QRS <40 μV (LAS <40), the root-mean-square voltage of the total QRS complex (RMS-QRS), the root-mean-square voltage of the last 40 ms (RMS-40), and the echocardiographically estimated left ventricular mass in healthy subjects.

The study group comprised 71 healthy volunteer medical residents, nurses and physicians (42 men, 29 women, mean age ± standard deviation 39 ± 13 years). None of the subjects had a history of heart or metabolic disease or systemic hypertension. They had normal physical examination, 12-lead standard electrocardiogram, and echocardiogram. No one was a professional athlete or had a body weight exceeding normal limits.

The signal-averaged electrocardiogram was recorded ≥15 minutes after bed rest and 2 hours after eating. All recordings were obtained with an Arrhythmia Research Technology 1200EPX high-resolution electrocardiograph. Standard orthogonal bipolar X, Y and Z leads were used to analyze a mean of 245 cycles (range 198 to 385) with a noise level ≤0.3 μV. The recorded signals were amplified, averaged and filtered with a Butterworth bidirectional filter (range 40 to 250 Hz). The signals obtained from the 3 leads were then combined to form a "vector magnitude," which is obtained by taking the square root of the sum of the squares ($V = \sqrt{X^2 + Y^2 + Z^2}$).

Signal-averaged QRS duration, LAS <40, RMS-QRS and RMS-40, all determined at 40-Hz high-pass filtering, were taken into consideration.

Echocardiography was performed with a Hewlett-Packard 77020 phased-array ultrasound unit, with a 2.25-MHz transducer. Left ventricular mass was calculated according to the formula of Devereux and Reichek[4]: left ventricular mass = $1.04\,[(LVID + VST + PWT)^3 - (LVID)^3] - 13.6$ *(in grams), where LVID is the left ventricular internal dimension, VST the ventricular septal thickness and PWT the posterior wall thickness.*

Means ± standard deviations were determined for the clinical, signal-averaged electrocardiographic and echocardiographic results. Comparison of means was made using Student's t *test for independent samples. The relation between late potentials and left ventricular mass was determined by the linear regression analysis.*

The means ± standard deviations of the clinical and signal-averaged electrocardiographic characteristics as well as estimated left ventricular mass are listed in Table I. A positive linear correlation was found between QRS duration and left ventricular mass ($r = 0.60$, $p = 0.0001$)*; only a weak positive linear correlation was found between LAS <40 and left ventricular mass* ($r = 0.30$, $p = 0.01$) *(Figure 1). A weak negative linear correlation was found between RMS-40 and left ventricular mass* ($r = -0.26$, $p = 0.03$)*, whereas no correlation was found between RMS-QRS and left ventricular mass (Figure 2).*

In a previous study conducted in healthy subjects, we found a correlation between the signal-averaged QRS duration and body size, particularly body height.[3] When the well-known relation between the echocardiographically determined left ventricular mass and body height[5] is taken into consideration, a prolonged filtered QRS dura-

TABLE I Clinical and Signal-Averaged Electrocardiographic Characteristics, and Left Ventricular Mass in 71 Healthy Subjects

Age (yr)	39 ± 13
Height (cm)	168 ± 9
Weight (kg)	68 ± 15
BSA (m²)	1.79 ± 0.19
Systolic BP (mm Hg)	123 ± 12
Diastolic BP (mm Hg)	78 ± 7
QRS duration (ms)	95 ± 10
LAS <40 (ms)	31 ± 9
RMS-QRS (μV)	71 ± 18
RMS-40 (μV)	37 ± 22
Left ventricular mass (g)	146 ± 42

Values are mean ± standard deviation.

BP = blood pressure; BSA = body surface area; LAS <40 = duration of the low-amplitude signals in the terminal portion of QRS <40 μV of amplitude; NS = not significant; QRS duration = signal-averaged duration of ventricular depolarization; RMS-40 = root-mean-square voltage of the last 40 ms of the signal-averaged QRS; RMS-QRS = root-mean-square voltage of the total QRS complex.

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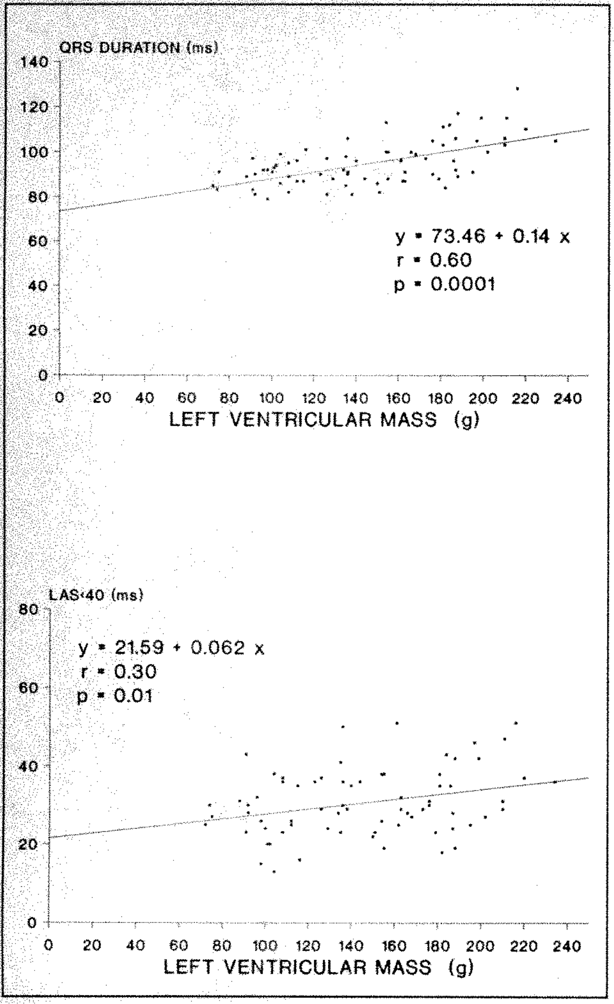

FIGURE 1. Linear correlation between signal-averaged filtered QRS duration and left ventricular mass *(top)* and between the duration of the low-amplitude signals <40 μV in the terminal portion of the QRS complex (LAS <40) and left ventricular mass *(bottom)*.

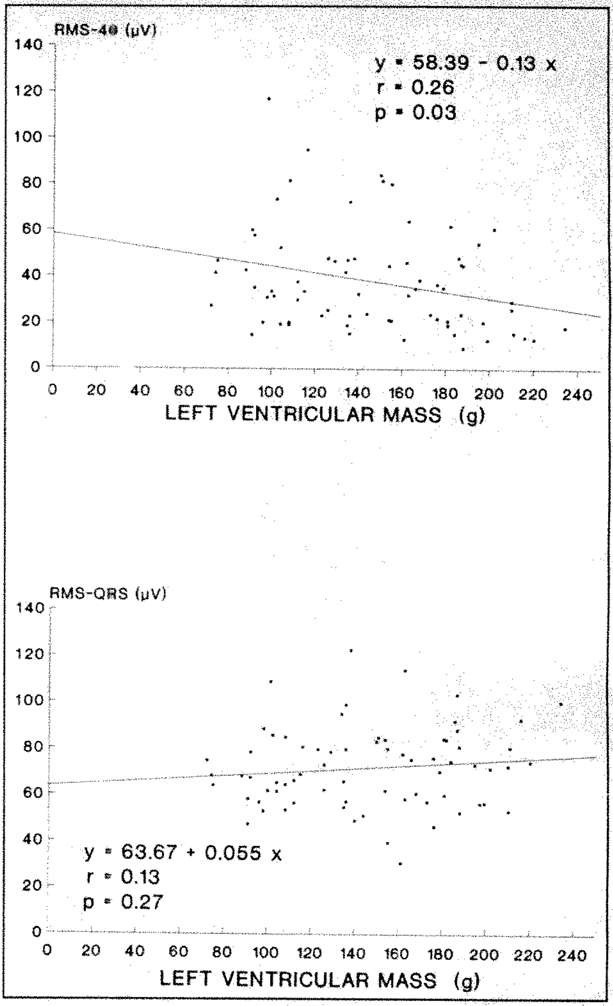

FIGURE 2. Linear correlation between the root-mean-square voltage of the low-amplitude signals in the last 40 ms of the QRS complex (RMS-40) and left ventricular mass *(top)* and between the root-mean-square voltage of the total QRS complex (RMS-QRS) and left ventricular mass *(bottom)*.

tion may thus represent not only the result of fragmented and delayed electrographic activity, but also the expression of a greater left ventricular mass. In fact, we found a positive linear correlation between QRS duration and left ventricular mass in healthy subjects. Only weak positive and negative linear correlations were found among LAS <40, RMS-40, and left ventricular mass, respectively.

In our laboratory and in most recent reports,[6] a value of QRS duration >114 ms, at 40-Hz high-pass filtering, is considered abnormal. In our 71 healthy subjects, we found 4 men (5.6%) and no women with a QRS duration >114 ms, but in these subjects left ventricular mass was greater when compared with that of subjects whose QRS duration was ≤114 ms (204 ± 13 vs 141 ± 42 g, $p = 0.004$). In healthy subjects, we found no correlation between RMS-QRS and left ventricular mass. This shows that the vector magnitude does not strictly express the quantity of myocardium that is depolarized. Only QRS duration has a good correlation with left ventricular mass and can therefore be associated with the quantity of myocardium that is activated. The weak correlations among LAS <40, RMS-40 and left ventricular mass indicate that these parameters do not depend solely on left ventricular mass, but that other electrophysiologic factors are involved in the genesis of low-amplitude signals at the end of the QRS complex.

In a healthy population, there is a significant linear relation between signal-averaged QRS duration and left ventricular mass, whereas there are only weak correlations among LAS <40, RMS-40 and left ventricular mass. The absence of correlation between RMS-QRS and left ventricular mass indicates that electrophysiologic aspects other than the mass of myocardium determine the height of the root-mean-square voltage of the total QRS complex. A prolonged, filtered QRS duration does not depend only on a delayed, fragmented and inhomogeneous electric activity, but is also the electrographic expression of a greater mass of myocardium.

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Epinephrine Versus Norepinephrine in Prehospital Ventricular Fibrillation

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According to the 1986 American Heart Association recommendations, epinephrine should only be given if ventricular fibrillation (VF) fails to respond to the first 3 consecutive direct-current shocks.[1] Animal experiments suggest that norepinephrine ($\alpha_{1,2}$; β_1 agonist) seems to be superior to epinephrine ($\alpha_{1,2}$; $\beta_{1,2}$ agonist) for improving myocardial hemodynamics during cardiopulmonary resuscitation.[2-4] Because there are only case reports about the use of norepinephrine in the cardiac arrest victim,[5] we compared norepinephrine with epinephrine in patients with out-of-hospital VF.

A consecutive series of 50 patients with out-of-hospital VF were enrolled in the study when 3 rapidly and consecutively administered direct-current shocks (200, 300, 360 J) failed to convert VF. Epinephrine (1 mg) and norepinephrine (1 mg) ampules of identical appearance were arranged using random numbers and were used consecutively. This prospective study was approved by our institutional committee on human experimentation. Cardiopulmonary resuscitation was performed by an emergency physician strictly according to the 1986 American Heart Association recommendations. The drug was injected into a peripheral vein or into the external jugular vein. Another shock (360 J) was performed 60 to 90 seconds after drug administration. When the first catecholamine dose failed to restore spontaneous circulation, all patients were resuscitated according to the guidelines for advanced life support. Patients who initially failed to respond to drug treatment but who later responded to continued conventional advanced life support were included in the outcome data. Resuscitation was considered to have been initially successful when, with or without dopamine therapy, the hemodynamic state of the patient was stable for ≥ 12 hours (systolic blood pressure >80 mm Hg). To test significance, a 2-tailed chi-square test was used for nominal data and Student's t *test for interval data. A p value <0.05 was considered statistically significant. All values are mean ± standard deviation.*

No significant demographic differences were found between the epinephrine ($n = 25$) and norepinephrine ($n = 25$) groups: mean age 68.2 ± 12.4 and 63.8 ± 11.6 years, male to female ratio 9:25 and 8:25, witnessed arrest 14 and 12, response time (time from call for help to physician arrival) 5.8 ± 3.0 and 5.4 ± 2.6 minutes. Witnessed arrest was defined as occurring when the collapse was directly seen or heard. Before the arrival of the emergency physician, 10 patients in the epinephrine and 11 in the norepinephrine groups received cardiopulmonary resuscitation. All patients had evidence of underlying cardiac disease. The external jugular approach was used in 9 of the epinephrine and in 10 of the norepinephrine groups. There was no difference in results between the external jugular and peripheral venous cannulation. The time required for intravenous cannulation was approximately 2 minutes after the diagnosis of cardiac arrest. Of the 50 patients investigated, 24 (48%) were successfully resuscitated, whereas 26 (52%) died at the site of the emergency. Patients were statistically more likely to be resuscitated if given norepinephrine. An initial resuscitation success was achieved in 6 of 25 patients after epinephrine and defibrillation and in 14 of 25 patients after norepinephrine and defibrillation. As a result of the fourth shock, asystole and electromechanical dissociation were observed in 5 of 25 epinephrine and in 6 of 25 norepinephrine patients. Fourteen epinephrine and 5 norepinephrine patients stayed in VF after the fourth shock. Resuscitation rates after the advanced life support sequence were also significantly higher in the norepinephrine (16 of 25) than in the epinephrine group (8 of 25). In the epinephrine group, the duration of resuscitation, until spontaneous circulation was restored, was <10 minutes in 6 patients and between 10 and 20 minutes in 2 patients. In the norepinephrine group, spontaneous circulation was regained in 15 patients in <10 minutes, with only 1 patient having a resuscitation time of between 20 and 30 minutes. There was a trend toward a higher hospital discharge rate in the norepinephrine (6 of 25) than in the epinephrine group (4 of 25). In the first 60 minutes after cardiopulmonary resuscitation, ventricular dysrhythmias were observed in 6 of 8 epinephrine and in 8 of 16 norepinephrine patients. Lidocaine had to be given to 6 of 16 patients in the norepinephrine group, but to no patient in the epinephrine group. Two patients in

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each group rearrested in the first hour after cardiopulmonary resuscitation, both developing VF, which was converted into a stable rhythm after 2 direct-current shocks of 200 and 300 J, respectively.

Early delivery of defibrillation is most important for successful resuscitation of patients with VF. If VF is still present after the third shock, epinephrine is recommended to increase coronary perfusion pressure and hence myocardial blood flow, in order to achieve a better basis for defibrillation and restoration of spontaneous circulation.[1] A number of vasopressor agents for improving myocardial oxygen delivery during cardiopulmonary resuscitation have been tested in animal experiments.[4] Studies comparing epinephrine and norepinephrine in pigs suggest that improvement in myocardial hemodynamics appears to occur when β_2 agonist properties are lacking or minimal.[3] We showed, in pigs with VF, that, for restoration of spontaneous circulation, norepinephrine was effective in a significantly shorter time than was epinephrine.[6] Epinephrine and norepinephrine in a dose of 1 mg led to the same increase in coronary perfusion pressure. In our investigation, defibrillation after norepinephrine administration led to a higher resuscitation success rate than after epinephrine. As observed in animal experiments, norepinephrine led to a higher incidence of ventricular dysrhythmias requiring lidocaine treatment in the first minutes after resumption of spontaneous circulation.[4] Rearrest frequency was not different between the groups. This may also have been influenced by lidocaine treatment.

Certain limitations must be taken into consideration when interpreting this study. The equipressor dose of epinephrine and norepinephrine during cardiopulmonary resuscitation in humans is not known. We do not know whether we would have achieved the same results with a different dose of epinephrine or norepinephrine. Because no previous blinded investigation of norepinephrine for resuscitation of the fibrillating human heart is available, we used only 1 norepinephrine dose in our algorithm. Furthermore, nothing is known about the pharmacokinetics of repeated norepinephrine administration during cardiopulmonary resuscitation in humans and the possibility of severe cardiac dysrhythmias in the immediate phase after resuscitation. We conclude that the use of norepinephrine in the treatment of VF may be superior to epinephrine, but the optimal dose and the time interval for repeated administration have yet to be determined.

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Transcatheter Laser-Assisted Balloon Pulmonary Valve Dilation in Pulmonic Valve Atresia

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In patients with pulmonary atresia (with or without a ventricular septal defect), a series of operations are required to achieve complete repair. These often include an initial systemic to pulmonary artery shunt, followed by a pulmonary valvotomy or a patch or a conduit to establish right ventricle to pulmonary artery continuity, and by closure of the shunt and correction of any other defects.

With the advent of newer interventional techniques, a number of congenital anomalies can be treated without surgery. Until now, pulmonic valve atresia was considered to lie beyond the scope of such interventional transcatheter treatment, because of the inability to perforate the atretic valve safely. We report our initial experience of transcatheter laser-assisted pulmonic valve dilation in 5 children with pulmonic valve atresia.

Transcatheter laser-assisted pulmonic valve dilation was attempted for pulmonic valve atresia in 5 children aged between 5 days and 2 years (Table I). All had pulmonic valve atresia, with confluent central pulmonary arteries: 2 had an associated ventricular septal defect (patients 1 and 2) and 3 had an intact ventricular septum (patients 3 to 5). In patient 1, the central pulmonary arteries were also supplied by major aortopulmo-

TABLE I Clinical Data

Pt. No.	Age	Weight (kg) & Sex	Diagnosis	Prior Surgery	Laser Route	Balloon Size (mm)
1	2 (yr)	9.1/M	PVA, VSD	RBTs	RV	3,5,7
2	2 (wk)	3.3/M	PVA, VSD	LBTs	BTs	5,7
3	5 (day)	2.1/F	PVA, PDA	0	RV	3,5
4	10 (wk)	3.2/M	PVA, PDA	0	RV	—
5	40 (wk)	6.7/M	PVA	LBTs	BTs	3.5,5,7

LBTs = left Blalock-Taussig shunt; PDA = patent ductus arteriosus; PVA = pulmonic valve atresia; RBTs = right Blalock-Taussig shunt; RV = right ventricle; VSD = ventricular septal defect.

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nary collateral arteries. A modified right Blalock-Taussig shunt with a 6-mm graft had been performed when patient 1 was aged 17 months. Patient 2 underwent a modified left Blalock-Taussig shunt with a 5-mm graft. In patients 3 and 4, the right ventricle was hypoplastic and both patients were dependent on the ductus arteriosus. Patient 5 also had a hypoplastic right ventricle and had a modified left Blalock-Taussig shunt with a 5-mm graft when he was 2 days old. When he was 10 months old, he developed increasing cyanosis, hepatomegaly and ascites because of a restrictive foramen ovale that resulted in a dilated right atrium and a moderate pericardial effusion.

Cardiac catheterization was performed percutaneously by the femoral venous and arterial routes under general anesthesia in all patients. Usually a 5 or 6Fr multipurpose catheter was inserted through the venous sheath and a 5Fr multipurpose catheter through the arterial sheath. Angiography was performed in the right ventricular body or infundibulum, in the anteroposterior and lateral projections through the venous catheter. The arterial catheter was positioned in the main pulmonary artery through the Blalock-Taussig shunts in 3 patients and through the ductus arteriosus in 2. Angiography was performed in the pulmonary artery in the same projections. The pulmonary valve ring diameter was measured angiographically. In each patient, the venous and arterial catheters were positioned close to the valve: 1 was used to pass the laser guidewire and the other was used as a landmark. The laser wire consisted of a 0.018-inch Teflon™-coated guidewire, containing a 116-μm optical fiber and terminating in a 0.5-mm metal tip. The optical fiber was interfaced with a Nd-YAG laser generator (Cardiolase 4000, Trimedyne Inc., Santa Ana, California). In 3 patients (nos. 1, 3 and 4), the laser wire was introduced anterogradely and in 2 (nos. 2 and 5) retrogradely. The laser wire was passed a few millimeters beyond the catheter tip until it was in contact with the valve. The laser energy was delivered continuously at 3.5 W as the wire was advanced across the valve. Once the laser wire was across the valve, a predilating catheter was passed over it, and this was followed by serial dilation of the valve using appropriately sized balloons for the pulmonary valve anulus (Table I). Figures 1 and 2 show some of the details in patients 3 and 5, respectively. In patient 4, the laser wire did not cross the valve and entered the pericardial cavity. No further attempts were made to cross the valve.

Successful laser-assisted pulmonic valve dilation was accomplished in 4 patients (nos. 1, 2, 3 and 5) in whom the laser wire crossed the valve after delivery of energy for 3 to 5 seconds. The duration of the procedure was 3.5 to 5 hours. There was an increase in pulmonary artery pressure or a decrease in right ventricular pressure, with little change in systemic arterial pressure (Table II). Afterward, patients 1, 2 and 5 were ventilated in the intensive care unit for 1 to 3 days before being returned to the ward. Patient 1 was discharged after 2 days, patient 2 after 10 days and patient 5 after 2 weeks. In patient 3, shortly after the laser wire was snared in the descending aorta, cardiac tamponade developed, which responded to percutaneous needle pericardiocentesis. After hemodynamic stability had returned, dilation with balloon catheters was achieved uneventfully. Two days later, the arterial duct had become smaller, despite continuation of prostaglandin infusion, and balloon dilation of the duct was therefore performed with a 3.5-mm balloon catheter. Patient 3 was extubated 15 days later. In patient 4, who had coexistent infundibular atresia, the laser wire passed into the pericardium from the infundibulum and caused immediate cardiac tamponade, which responded to needle aspiration. After hemodynamic stability was achieved, this patient underwent a systemic to pulmonary artery shunt operation, but died on the operating table.

During a short 2- to 6-month follow-up of the 4 successful patients, the Doppler-estimated pressure drop across the right ventricular outflow ranged between 50 and 70 mm Hg, and there was evidence of pulmonary regurgitation in all patients. In patient 5, the pericardial

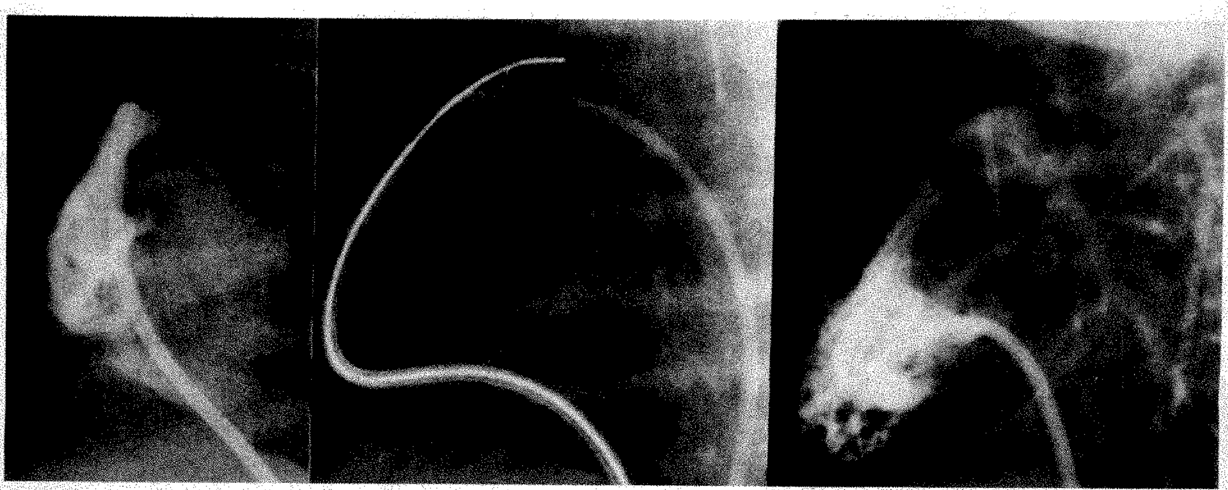

FIGURE 1. Right ventricular angiogram in the left lateral projection showing pulmonic valve atresia. Catheter positioned in the main pulmonary artery has been passed through the arterial duct *(left)*. In the *middle panel*, the laser wire has been advanced across the pulmonary valve through the right ventricular catheter. After balloon dilation, right ventricular angiogram *(right)* shows anterograde flow across the pulmonary valve.

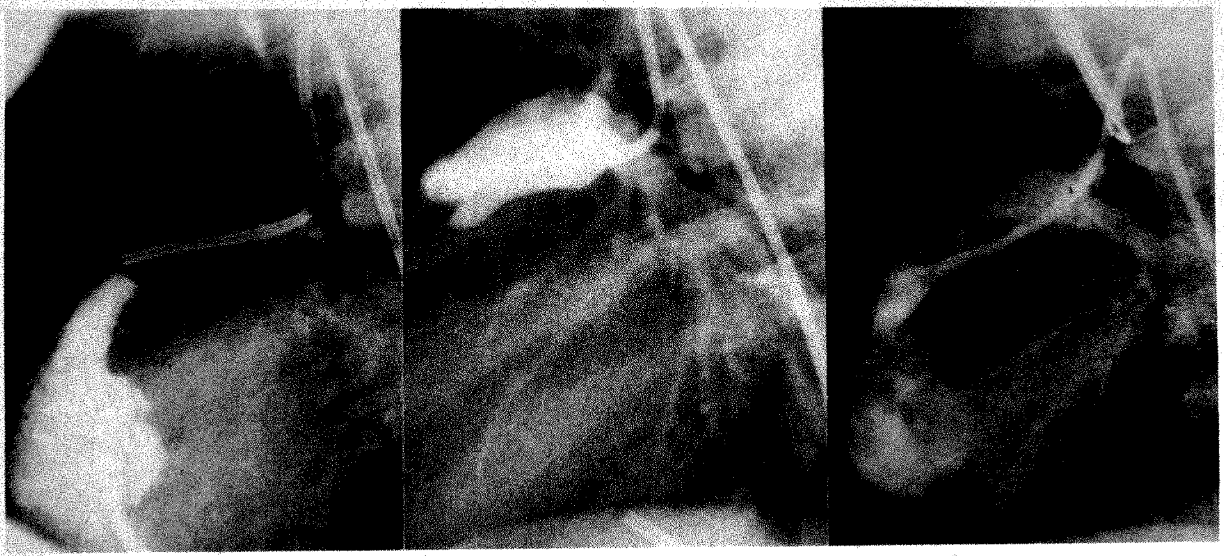

FIGURE 2. Right ventricular angiogram *(left)* and angiogram in the main pulmonary artery *(middle)* define the landmarks. After laser-assisted pulmonary valve dilation, right ventricular angiogram *(right)* shows forward flow into the pulmonary artery.

effusion and ascites resolved. Transcutaneous oxygen saturations in the 4 patients ranged from 70 to 87% and, in patient 3, the ductus arteriosus had closed.

The first cardiac laser application was for an intraoperative pulmonary valvotomy in 1974.[1] Since then, several investigators have evaluated the technique experimentally,[2,3] but not clinically in children. In adults, bare fiber laser and "hot tip" laser thermal probes have been used to recanalize peripheral artery occlusions with variable success.[4,5]

In patients with pulmonary atresia and an intact ventricular septum, the hospital mortality for palliative operations (shunt with or without valvotomy) is approximately 10%.[6] Some patients may require further palliative operations, either during the same admission or over the next few years. The subsequent definitive repair may have a hospital mortality rate of 25 to 50%.[6] In patients with pulmonary atresia associated with a ventricular septal defect, major aortopulmonary collateral arteries and confluent central pulmonary arteries, a staged surgical approach is frequently required in order to achieve a complete repair. The 10-year survival rate in the series reported by Kirklin et al[7] was 69% in this group of patients.

TABLE II Pressures (mm Hg) Before and After Pulmonic Valve Dilation

Pt. No.	Right Ventricle(s)		Pulmonary Artery (s/d)		Aorta (s/d)	
	Pre	Post	Pre	Post	Pre	Post
1	105	110	17/12	36/16	106/43	115/45
2	120	100	21/17	45/15	100/55	96/50
3	135	85	60/25	60/25	90/27	85/25
4	115	*	22/7	*	110/40	*
5	190	90	15/11	26/20	96/34	90/40

* Unsuccessful valve dilation.
d = end diastole; s = peak systole.

In this small preliminary series, our initial objective was to determine whether laser-assisted valve dilation could establish anterograde flow across the atretic pulmonic valves. In the long term, we need to establish whether the right ventricle and pulmonary artery will increase in size. Some of our initial patients had already undergone palliative shunts, and their outflow tract anatomy was considered suitable for the future creation of surgical right ventricular to pulmonary artery continuity. In our first 2 patients, having established anterograde flow across the pulmonary valve, we hoped to achieve closure of the ventricular septal defect without an interim operation on the right ventricular outflow tract. Thus, we were encouraged to attempt laser-assisted pulmonic valve dilation and dilation of the ductus arteriosus in order to avoid any palliative surgery in patients with pulmonary atresia and an intact ventricular septum. Patient 3 has thus far avoided any form of palliative surgery and we are monitoring her right ventricular function. Although patient 5 had a surgical shunt established in the neonatal period, this patient may likewise not need further operations, as the shunt could be occluded nonsurgically when indicated. In retrospect, we feel that patient 4 was unsuitable for laser-assisted pulmonic valve dilation, because of the combination of infundibular and pulmonic valve atresia. This reduced the safety margin when the laser guidewire was directed toward the pulmonary artery.

We believe that our first objective of establishing anterograde flow across the pulmonic valve has been achieved and that laser-assisted valve dilation is feasible in neonates, infants and children with pulmonic valve atresia. However, it should be avoided in those with associated infundibular atresia. Further follow-up is needed to determine whether our long-term objectives can be achieved by this approach.

Acknowledgment: We thank Trimedyne Inc. for providing us with the laser guidewires, Paul V. L. Curry, MD, of Guy's Hospital, and David C. Cumberland, MD, of Northern General Hospital, Sheffield, United Kingdom, for their helpful advice, and Deo Persaud, Cordis, United Kingdom, for providing technical assistance.

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Atherectomy of Right Coronary Ostial Stenoses: Initial and Long-Term Results, Technical Features and Histologic Findings

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Coronary angioplasty of lesions involving the right coronary ostium has been limited by suboptimal early success and by high rates of both acute complications and late restenosis.[1] In nonostial stenoses, directional coronary atherectomy appears to result in larger residual coronary dimensions than does coronary angioplasty[2] and may provide a potentially improved long-term outcome. To determine the immediate and long-term angiographic results of directional atherectomy in patients with right ostial stenoses, we attempted this procedure in 7 consecutive patients with coronary stenoses within 3 mm of the right coronary ostium.

Seven patients with New York Heart Association functional class III to IV angina were referred to the University of Michigan Medical Center for nonsurgical revascularization of stenoses involving the right coronary ostium. One to 4 months before detection of the ostial stenoses, 3 patients had coronary angioplasty of the midright coronary artery. After intracoronary nitroglycerin, all patients had a stenosis >50% in diameter within 3 mm of the orifice of the right coronary artery.[1]

After informed consent and pretreatment with aspirin, a calcium antagonist and 10,000 to 15,000 U of intravenous heparin, a 9.5 to 11Fr guiding catheter (Devices for Vascular Intervention, Inc., Redwood City, California) was advanced to the right coronary ostium. A 0.014-inch coronary guidewire was positioned across the coronary stenosis and predilation performed with an undersized standard angioplasty balloon (Figure 1). A 5 to 7Fr atherectomy device (Devices for Vascular Intervention, Inc.) was then positioned across the right coronary ostium and the guiding catheter was withdrawn into the ascending aorta. Coronary atherectomy was then performed by the method previously described[3] until a satisfactory angiographic result was obtained. Patients were monitored for evidence of abrupt closure and intravascular sheaths were removed within 12 hours. Successful atherectomy was defined as a <50% residual stenosis, tissue removal and the absence of in-hospital ischemic complications. At the time of hospital discharge, patients were maintained on aspirin and a calcium antagonist. Repeat coronary arteriography 6 months after the procedure was recommended.

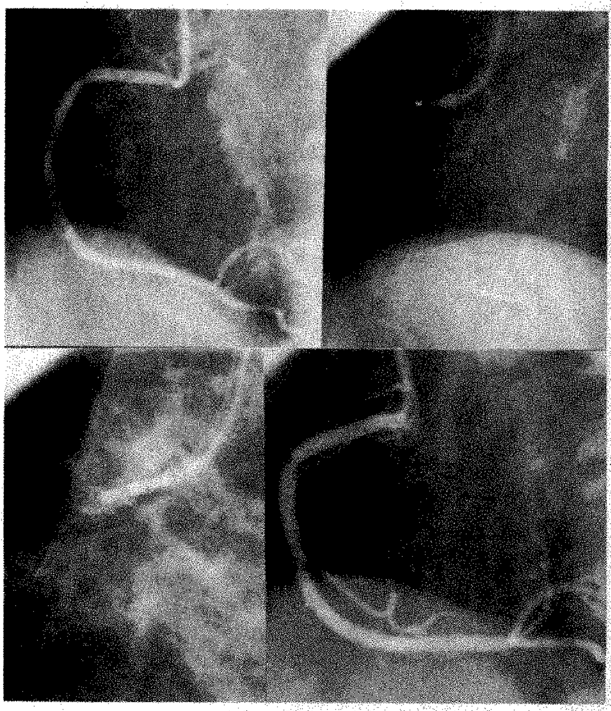

FIGURE 1. *Top left,* left anterior oblique projection of a right coronary ostial lesion. Note streaming artifact from inability to fill the distal vessel adequately. *Top right,* after predilation with an undersized balloon catheter, the atherectomy device is positioned in the coronary ostium and the guiding catheter is withdrawn slightly *(lower left).* The coronary ostium is widely patent immediately after coronary atherectomy *(lower right).*

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TABLE I Angiographic Results in Patients with Successful Right Coronary Ostial Atherectomy

Patient	Age (yr) & Sex	Coronary Calcium (0–3+)	Lesion Length (mm)	Percent Diameter Stenosis (minimal diameter [mm]) Before (MD mm)	After (MD mm)	Follow-Up (MD mm)
1	67 M	1+	2.0	63 (1.8)	17 (3.4)	18 (2.8)
2	72 F	2+	1.4	56 (2.1)	0 (4.0)	13 (3.1)
3	62 M	2+	11.1	72 (1.1)	46 (1.7)	78 (0.7)
4	45 M	2+	3.3	58 (1.8)	0 (4.1)	10 (4.3)
5	72 F	0	1.0	59 (2.0)	17 (3.3)	0* (2.4)
6	78 M	1+	2.0	59 (1.2)	6 (2.8)	10 (2.4)
Overall				61 ± 5 (1.7 ± 0.4)	14 ± 16 (3.2 ± 0.8)	22 ± 26 (2.6 ± 1.1)

* Slight aneurysmal dilatation at the site of atherectomy.
Values are expressed as mean ± standard deviation.

Coronary calcific deposits were graded qualitatively on a 0 to 3 scale, with 0 representing no calcific deposits and 1+, 2+ and 3+ representing mild, moderate and extensive calcific deposits, respectively. End-diastolic images obtained from the left anterior oblique projection demonstrating the right coronary ostium were used for quantitative coronary analysis, with a computer-assisted automated edge detection system.[4]

After formalin fixation, a hematoxylin/eosin stain was used to assess overall cellularity and specimen morphology. VanGieson/elastin and modified trichrome/fibrin stains were used to evaluate normal vascular components beyond the internal elastic lamina and thrombotic components, respectively. Quantitative histomorphometric analysis was performed manually on images projected onto a magnetized digitizing tablet. Specimen components were divided into normal vessel wall containing the media, adventitia, lesion and thrombus. The lesion comprised (1) sclerotic, dense collagenic tissue with only scant cellularity, with or without calcification, (2) fibrocellular areas with abundant viable cells, smooth muscle and macrophages, and (3) lipid-rich regions with necrosis and an amorphous extracellular matrix. Each specimen was planimetered in square millimeters and expressed as a percentage of the total specimen area.

TABLE II Histologic Findings in Patients Undergoing Right Ostial Atherectomy

Patient	Vessel Wall Adventitia (%)	Media (%)	Atherosclerotic Plaque FC (%)	SCL (%)	LD (%)
1	5	20	27	41	7
2	0	15	59	0	26
3	0	25	31	23	21
4	0	0	30	32	0*
5	2	25	31	37	5
6	0	2	58	37	0*
Overall	1 ± 2	15 ± 10	39 ± 14	28 ± 14	10 ± 10

* Remaining percent thrombus.
Values are mean ± standard deviation.
FC = fibrocellularity; LD = lipid-rich deposits; SCL = sclerotic.

Two-dimensional intracoronary ultrasound imaging of the right coronary ostium was performed before and after coronary atherectomy in 1 patient with a 4.8Fr, 20-MHz catheter-based imaging transducer (Boston Scientific/Diasonics, Watertown, Massachusetts).

Successful coronary atherectomy of the right coronary ostium was performed in 6 of 7 patients. In the remaining patient, despite successful predilation with standard coronary angioplasty, a 6Fr atherectomy device could not be positioned across the stenosis because the 9.5Fr guiding catheter provided insufficient backup. No patient developed in-hospital ischemic complications.

In patients with successful atherectomies, the percent diameter stenosis was reduced from 61 ± 5 to 14 ± 16% and the minimal luminal diameter increased from 1.7 ± 0.4 to 3.2 ± 0.8 mm (Table I). Coronary arteriography was repeated in all patients 6.2 ± 2.7 months after successful atherectomy. One patient with an initial lesion length of 11.1 mm, coronary calcific deposits and a residual 46% stenosis immediately after coronary atherectomy developed angiographic restenosis (follow-up percent diameter stenosis, 78%). None of the remaining patients developed restenosis.

A total of 4 to 16 tissue fragments were obtained per specimen. Normal vessel wall was identified in 5 of 6 patients; 2 of these also had small amounts of adventitia (Table II). The major lesion components were fibrocellular (39 ± 14%) and sclerotic (28 ± 14%). Lipid-rich components were infrequent (10 ± 10%), and thrombus was rarely seen.

After predilation with standard coronary angioplasty methods, intracoronary imaging demonstrated extensive intimal thickening and atheroma in the region of the right coronary ostium (Figure 2). After coronary atherectomy, an asymmetric resection of the ostial lesion was identified, but significant residual atheroma was still noted.

The precise mechanism whereby coronary atherectomy results in improved coronary dimensions remains controversial.[3,5] Whereas atheroma resection mediates at least some of these improvements in coronary dimensions, other mechanisms, such as mechanical dilatation by the

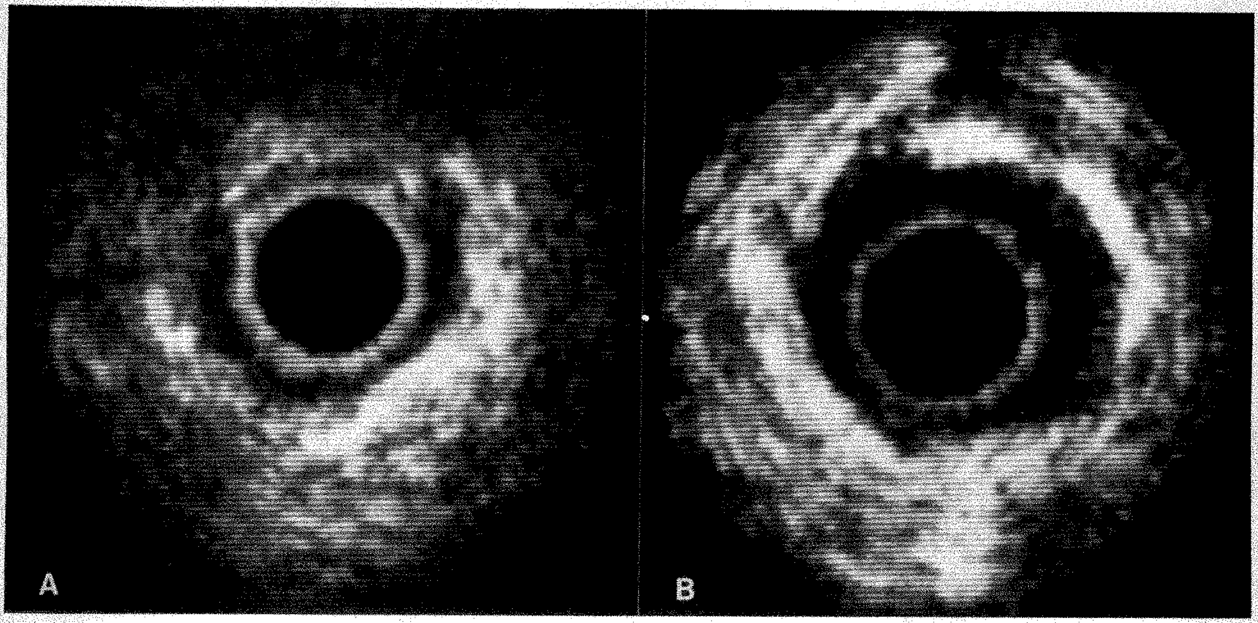

FIGURE 2. Two-dimensional intracoronary ultrasound image of the right coronary ostium after coronary angioplasty. *A*, the imaging catheter with "ring-down" artifact is positioned in the center of the image. A hyperecho region is noted from 1 to 6 o'clock and is consistent with thickened intima and atheroma. Echo "drop-out" is seen from 10 to 12 o'clock as a result of coronary calcification. *B*, after directional atherectomy, the residual lesion in the coronary lumen has a scalloped appearance. Despite marked improvement in coronary dimensions, significant atheromatous tissue remains.

atherectomy device and barotrauma resulting from the unilateral balloon inflation, may also be operative.[3,5] Using quantitative angiographic methods after coronary atherectomy, Safian et al[3] demonstrated that the weight of tissue retrieved from the atherectomy device is insufficient to account fully for the angiographic improvement. In the present series, 4 to 16 tissue fragments were retrieved per specimen. Although not rigorously weighed, the size of the fragments was also insufficient to account for all of the improvement in coronary dimensions. Furthermore, despite the presence of media in 5 of 6 specimens, residual atheroma was observed with intracoronary ultrasound, suggesting that atheroma resection by coronary atherectomy is incomplete. Although the safety of deep tissue resection has been reported,[6] more aggressive attempts at complete atheroma resection may result in coronary perforation[7] without angioscopic or ultrasound guidance.[8]

Whereas restenosis after standard coronary angioplasty may occur more frequently in patients with right ostial stenoses than in other coronary lesions,[1] restenosis has also been reported in nonostial stenoses after coronary atherectomy.[3] Although randomized trials will be required to compare the long-term results of these 2 techniques for restenosis, the results of this pilot trial are encouraging. Further study into the role of coronary atherectomy in patients with right ostial stenoses is suggested.

In patients with right ostial stenoses, technical difficulties with guiding catheter intubation, lack of adequate backup, and inability to pass balloon dilatation catheters across the stenosis are major limitations seen with both coronary angioplasty and atherectomy. Further refinement in guiding catheter and device profile may result in improved procedural success rates. Furthermore, the adjunctive benefit of coronary atherectomy may be difficult to determine if predilation with standard coronary angioplasty is required. In the majority of patients in this pilot series, intraluminal haziness prevented application of standard computer-assisted edge detection algorithms to lesions after balloon dilatation. After coronary atherectomy, the arterial borders were more distinct, allowing application of the quantitative arterial program. Thus, in addition to its effects secondary to balloon dilatation, adjunctive atherectomy may permit removal of intracoronary debris and potentially provide a less platelet-reactive surface for subsequent platelet aggregation and thrombosis.

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Insights into the Mechanism of Luminal Improvement After Directional Coronary Atherectomy

William F. Penny, MD, Dwayne A. Schmidt, MD, Robert D. Safian, MD, Raymond E. Erny, MD, PhD, and Donald S. Baim, MD

Directional coronary atherectomy (DCA) is effective in improving the luminal diameter of diseased peripheral and coronary arteries.[1-3] The luminal improvement afforded by DCA is presumed to result primarily from tissue removal,[4] but the contribution of concomitant mechanical dilation has not been determined. To study the mechanism of coronary lumen enlargement by DCA, we examined the relation between the amount of tissue retrieved and the change in vessel caliber after atherectomy.

Patients undergoing DCA at Beth Israel Hospital between February 1989 and April 1990 were enrolled in this study. The atherectomy catheter used (Simpson AtheroCath®, Devices for Vascular Intervention, Inc., Redwood City, California) consists of a rotating cup-shaped cutter housed within a windowed cylinder, with an opposing 2.0-mm balloon that may be inflated to a pressure of up to 40 pounds per square inch during cutter advancement. Selection of device size (6 or 7Fr) was based on the diameter of the reference segment, with the number of passes determined by the amount of residual stenosis after initial atherectomy cuts, as previously described.[1] A successful atherectomy was defined as: (1) tissue removal, (2) residual vessel stenosis <50% after atherectomy without resort to angioplasty, and (3) the absence of major complications (death, Q-wave myocardial infarction or emergency bypass surgery).

Tissue specimens retrieved from the device capsule during atherectomy of native coronary artery or saphenous vein bypass graft stenoses were placed on a Telfa™ pad to adsorb adherent fluid and then transferred immediately to sealed, previously weighed vials containing normal saline. Tissue weights were subsequently determined using a Mettler analytic balance, and tissue volume was estimated from the incremental vial weight, assuming a tissue specific gravity of 1.0 mg/mm^3. In each case, the tissue was then fixed in formalin and submitted for pathologic analysis.

Angiograms of the vessel segment were obtained before and after atherectomy in all cases. Frames that demonstrated the vessel stenosis at its most severe were paired with identical projections obtained after atherectomy. The angiographic lumen was hand-traced and planimetered from optically magnified projections of the angiographic frame, and dimensions were calculated using the guiding catheter as a reference. The increase in luminal volume was then estimated, assuming a cylindric cross section and using an area-length calculation applied to views both before and after atherectomy (Figure 1). Change in luminal volume was calculated as the difference between luminal volume before and after atherectomy in cubic millimeters. In a subset of 11 patients, biplane luminal volume was also calculated as the average of the values determined from 2 separate views. Diameter stenosis before and after atherectomy was also determined with digital calipers (Digital Electronic Calipers, Sandhill, Inc., Littleton, Colorado).

An "atherectomy index" was calculated for each patient as the ratio of removed tissue volume to the change in luminal volume. An index of 1.0 would thus correspond to "pure" atherectomy, in which all luminal improvement was due to tissue removal. An index of zero would correspond to pure dilation, and values between 0 and 1.0 to combinations of tissue removal and dilation.

Fifty-six patients underwent DCA during the study period. Tissue specimen weights were obtained in 46 patients, 39 of whom were included in the investigation. Seven patients were excluded: 2 with inadequate angiographic data, 2 with tissue weight determination reflecting >1 lesion, 2 in whom luminal volume estimation was complicated by vessel branching, and 1 in whom atherectomy was unsuccessful.

The atherectomy procedures in the 39 study patients were successful in reducing mean luminal stenosis from 77 ± 12 to 4 ± 17%. Thirty-five procedures were performed in native coronary arteries (31 left anterior de-

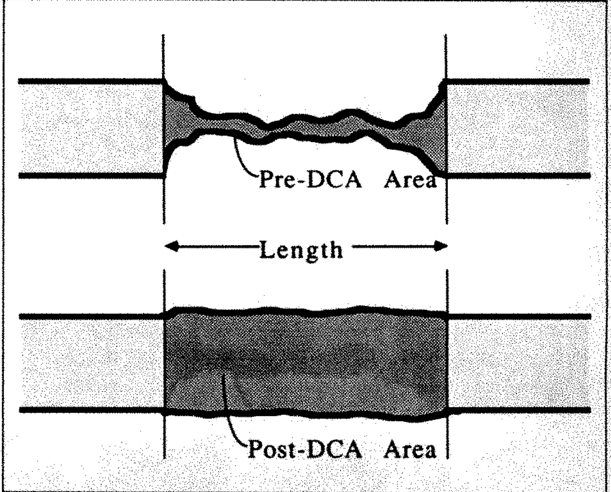

FIGURE 1. Change in luminal volume was estimated by assuming a cylindric cross section and applying an area-length calculation to views before (Pre-DCA) and after (Post-DCA) direct coronary atherectomy.

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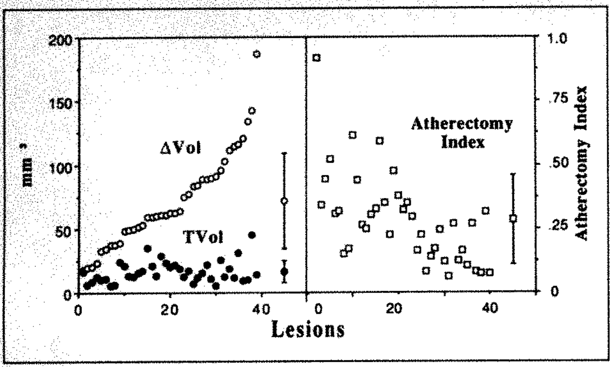

FIGURE 2. ***Left,*** **volume of tissue removed (TVol–*closed circles*) versus the corresponding change in lumen volume (ΔVol–*open circles*) for each lesion. *Right,* corresponding atherectomy index (TVol/ΔVol) for each lesion.**

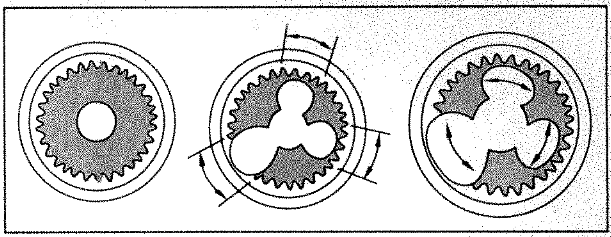

FIGURE 3. Schematic of the proposed mechanism for improvement in vessel lumen by a combination of atherectomy and facilitated mechanical angioplasty.

scending, 4 left circumflex) and 4 in saphenous vein bypass grafts, with a mean reference vessel diameter of 2.9 ± 0.7 mm. Calculated change in luminal volume ranged from 19 to 186 mm^3 (mean 72 ± 37 mm^3). Biplane volume measurements calculated using the average of 2 separate views in a subgroup of 11 patients did not differ significantly from values derived from single-view measurements. All volume determinations were thus based on a single "worst view" analysis. Tissue weights ranged from 6 to 45 mg (mean 16.5 ± 8.5 mg). The mean atherectomy index was 0.28 ± 0.18, ranging from 0.07 to 0.92 (Figure 2), with no correlation between the volume of tissue retrieved and the change in luminal volume ($r = 0.13$, difference not significant), or between atherectomy index and reference vessel size ($r = 0.19$).

DCA provides effective revascularization of stenotic peripheral and coronary arteries and vein grafts, affording less residual stenosis than that usually achieved by conventional balloon angioplasty. Although it has been stated[4] that the fundamental mechanism of DCA is the excision of the plaque encroaching upon the vessel lumen, tissue removal may not account for *all* of the observed improvement in luminal dimensions. Alternatively, a significant component of the lumen enlargement might result from mechanical dilation, either by the "Dotter" effect, associated with passage of the high-profile (2 to 2.5 mm) atherectomy device, or by the low pressure (20 to 40 psi) balloon inflations performed during cutter passes. This latter effect may be especially important once atherectomy cuts have extended to or through the internal or external elastic lamina, or both, increasing arterial compliance and enhancing susceptibility of the vessel to dilation by the atherectomy catheter balloon. Histologic analysis shows that deep cuts such as these are common in clinical atherectomy procedures.[1,5] Improvement in vessel lumen by a combination of atherectomy and "facilitated mechanical angioplasty" (Figure 3) would involve preferential expansion of the bases of the atherectomy cuts. Compared with the random cracking of plaque seen with conventional balloon angioplasty, preferential expansion may explain the relatively smooth angiographic appearance of vessels after atherectomy.

In the present study, 39 patients underwent successful DCA with the Simpson AtheroCath®, with improvement in luminal caliber and retrieval of atheromatous plaque from the vessel wall. In all cases, however, the improvement in luminal volume was greater than that which could be explained by the volume of tissue removed. The atherectomy index (which relates the amount of tissue removed to change in luminal volume) was thus <1.0 in all cases, and averaged 0.28 for the group as a whole. This finding suggests that the improvement in lumen seen after DCA results only *partially* from the removal of tissue from the vessel wall, with mechanical dilation playing an important adjunctive role. In fact, the atherectomy index was <0.5 in 35 of 39 cases, suggesting that the Dotter effect or balloon inflation, or both, accounts for most of the improvement in luminal volume.

The failure of atherectomy as currently performed to produce a decisive reduction in the rate of subsequent restenosis[1] may be related to this considerable amount of concomitant vessel dilation. Reduction in restenosis rate might require the development of devices that can safely remove more atheroma without relying on concomitant vessel dilation, possibly using intravascular ultrasonic guidance.[6]

Several limitations may have influenced the values calculated in this study. (1) Vessel segments with eccentric or irregular stenoses may appear to have a larger lumen in certain projections than is actually present. The selection of angiographic views to show each stenosis at its most severe tends to counteract this potential artifact in the views before DCA. (2) If the lumen cross section after atherectomy were markedly irregular or "cloverleafed," rather than circular, the luminal volume after the procedure might still be exaggerated by the angiogram, overestimating the true increase in luminal volume and artifactually lowering the atherectomy index. (3) The method used to calculate changes in luminal volume is geometrically sound, but has yet to be validated on appropriate phantom vessels. (4) We assumed an overall specific gravity of 1.0 for plaque, although calcific and lipid-laden components within the plaque have specific gravities above and below the assumed value of 1.0. Given the marked disparity between tissue and angiographic volumes, however, even 20% (e.g., 0.8 to 1.2) errors in assumed specific gravity or similar systematic errors in measured luminal volume would not significantly affect the overall observation that a significant portion of luminal improvement after coronary atherectomy results from mechanical dilation in addition to tissue removal.

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Acute Complications Associated with New-Onset Atrial Fibrillation

Harold Z. Friedman, MD, Scot F. Goldberg, MD, John D. Bonema, MD, David R. Cragg, MD, and Andrew M. Hauser, MD

Atrial fibrillation (AF) is a common cardiac arrhythmia having an estimated prevalence in the general population of 0.4%.[1] However, in patients aged >60 years, the prevalence increases to 2 to 4%.[2] The initial management of new-onset AF is controversial and varies among institutions and physicians. Because acute AF often occurs in elderly patients, and is frequently associated with serious organic cardiac disease,[3,4] these patients are often admitted to a monitored critical-care bed. The criteria for admission to a monitored cardiac unit have not been described. To identify clinical variables that might allow identification of patients at low and high risk for developing cardiovascular complications, all patients with symptomatic new-onset AF admitted from the emergency department to a telemetry or intensive care unit were prospectively studied.

All patients admitted from December 1987 to March 1989 to a medical telemetry or intensive care unit with, presumably, acute-onset AF were identified. This diagnosis was determined by the patient history, inspection of all available electrocardiograms and physician interview. Patients were excluded if AF occurred incidental to coexisting medical problems that would have independently necessitated hospitalization or if symptoms were present for >48 hours. Of 108 patients consecutively screened for enrollment, 9 were excluded from the study: 3 patients presented with respiratory failure requiring mechanical ventilation, 2 with theophylline toxicity, 2 with electrocardiographic evidence of acute myocardial infarction, 1 with a subarachnoid hemorrhage, and 1 in whom cardiopulmonary arrest had occurred. The remaining 98 patients constituted the study group.

Sixty-seven variables were assessed from information obtained during the admission history, initial physical examination, laboratory assessment, chest roentgenogram and electrocardiogram. M-mode and 2-dimensional echocardiographic data, serial total and serum creatine kinase–MB levels were also assessed. Duration of the arrhythmia, method of conversion to normal sinus rhythm and the occurrence of any clinical complications were evaluated daily. An adverse event was defined as any condition that developed which was potentially life-threatening or prolonged the hospital course.

The patients were subsequently assigned to 2 groups: a complicated group having ≥1 morbid event, and an uncomplicated group having a benign hospital course. Group t *test statistical analysis was applied to the continuous variables. The 1-sided Fisher exact test was applied to the remaining discrete variables. Multiple logistic regression analysis was also used to identify variables that would select patients at risk for developing complications. Statistical significance was defined as $p < 0.05$. All results are expressed as mean ± standard deviation.*

Mean age of the 98 study patients (52 men and 46 women) was 69 ± 14 years. Eighteen patients (18%) had a total of 46 clinical complications and they comprised the complicated group. Among these 18 patients, 10 developed new or progressive congestive heart failure, 9 hypotension (2 required emergency electrical cardioversion), 8 Lown class IV ventricular ectopy, 6 respiratory failure, 4 angina pectoris, and 1 had electrocardiographic evidence of myocardial infarction. No strokes or embolic phenomena occurred. Six patients (6.1%) died during hospitalization. The mean age of the complicated group was 75 ± 11 years and there were 11 men (61%) and 7 women (39%). Eighty patients (82%) (41 men [51%] and 39 women [49%]) had an uncomplicated hospital course and comprised the uncomplicated group. Mean age of this group was 68 ± 14 years ($p < 0.02$).

Among the 67 variables examined, 25 were identified by univariate analysis as significantly different between the groups (Table I). Variables found more frequently in the complicated group included advanced age, dyspnea, fatigue and history of smoking. Findings indicative of left ventricular dysfunction or congestive heart failure by history, examination or previous medical therapy were significantly more frequent in the complicated group. Chest roentgenography suggesting pulmonary edema or congestive heart failure, left bundle branch block on the initial electrocardiogram, echocardiographic evidence of left atrial enlargement (>40 mm) or severe left ventricular dysfunction, elevated total (more than twofold increase) and MB fraction creatine kinase levels, and unsuccessful conversion to normal sinus rhythm were linked with complications.

Complaints that were more frequent in the uncomplicated group included presyncope and palpitations. These

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patients were more apt to have normal chest roentgenographic and echocardiographic studies. Fifty-six patients in this group (70%) had successful conversion to normal sinus rhythm within 48 hours in contrast to only 8 patients (44%) in the complicated group.

Multiple logistic regression analysis showed that among all of the variables considered, the presence of increased jugular venous distension ($p < 0.005$), a mitral regurgitation murmur ($p < 0.05$), and elevation of creatinine kinase–MB fraction ($p < 0.02$) were significantly associated with an adverse outcome.

Digoxin was acutely administered to 73 patients (74%) and an additional 22 (23%) received other antiarrhythmic therapy. Treatment had no detectable effect on outcome. Cardiac diagnoses at the time of discharge are listed in Table II. Coronary heart disease with and without acute myocardial infarction accounted for 27% of all diagnoses. A diagnosis of acute myocardial infarction or cardiomyopathy of undetermined etiology was associated with greater risk for subsequent morbid events ($p < 0.02$ and $p < 0.03$, respectively). No underlying cardiac diagnosis was identified in 36 patients (36%).

TABLE I Clinical Variables Associated with Major Complications by Univariate Analysis

	Complication (n = 18)	No Complication (n = 80)	p Value
Age (years)	75 ± 11	68 ± 14	<0.02
Presyncope	2 (11%)	29 (36%)	<0.04
Dyspnea	14 (78%)	42 (53%)	<0.05
Palpitations	4 (22%)	40 (50%)	<0.03
Fatigue	10 (56%)	25 (31%)	<0.05
Nausea or vomiting	5 (28%)	46 (58%)	<0.03
History of heart failure	7 (39%)	4 (5%)	<0.0005
Smoking history	11 (61%)	22 (28%)	<0.01
Current digoxin use	6 (33%)	7 (9%)	<0.02
Current antiarrhythmic use	2 (11%)	0	<0.04
Jugular venous distension	7 (39%)	5 (6%)	<0.002
Peripheral edema	8 (44%)	14 (18%)	<0.02
Pulmonary rales	10 (56%)	21 (26%)	<0.02
Left bundle branch block	5 (28%)	3 (4%)	<0.005
Chest roentgenography			
Pulmonary edema or CHF	7 (39%)	12 (15%)	<0.05
Normal	8 (44%)	55 (69%)	<0.01
Creatine kinase			
Elevated total	9 (50%)	17 (21%)	<0.02
MB elevated	6 (33%)	9 (11%)	<0.04
Echocardiography			
Left atrium >40 mm	14 (78%)	35 (44%)	<0.005
Left ventricular function			
Normal	8 (44%)	51 (64%)	<0.04
Severe dysfunction	4 (22%)	4 (5%)	<0.05
Conversion to sinus rhythm			
<6 hours	3 (17%)	23 (29%)	NS
6–48 hours	5 (28%)	33 (41%)	<0.04
No conversion	8 (44%)	17 (21%)	<0.05

CHF = congestive heart failure; NS = not significant.

TABLE II Discharge Diagnoses

Diagnosis	Complication (n = 18)	No Complication (n = 80)	p Value
Coronary artery disease			
Without infarction	3 (17%)	13 (16%)	NS
Acute infarction	5 (28%)	5 (6%)	<0.02
Cardiomyopathy			
Alcoholic	2 (11%)	3 (4%)	NS
Idiopathic	5 (28%)	6 (8%)	<0.03
Systemic hypertension	0	9 (11%)	NS
Mitral valve disease	1 (6%)	4 (5%)	NS
COPD exacerbation	0	2 (3%)	NS
Postaortic valve surgery	0	1 (1%)	NS
Postcoronary bypass surgery	0	1 (1%)	NS
Sick sinus syndrome	0	1 (1%)	NS
Thyrotoxicosis	0	2 (3%)	NS
Acute alcohol ingestion	0	0	NS
None established	2 (11%)	33 (41%)	<0.02

COPD = chronic obstructive pulmonary disease; NS = not significant.

In our study, the mean age, sex distribution and final diagnoses are in accordance with previous acute AF studies.[1-4] However, these investigations have been either retrospective, involved small populations or failed to document in-hospital outcome. Previous work has also demonstrated that the traditional indicators of acute myocardial ischemia are reliably present in the setting of new-onset AF and predict greater adverse cardiovascular morbidity and mortality.[5-8] Consequently, patients displaying any evidence of myocardial ischemia or acute infarction were deliberately excluded. Nevertheless, 15% of patients did develop enzymatic evidence of non-Q-wave myocardial infarction demonstrating the importance of a conservative management strategy favoring admission of patients with an ischemic or atypical history of chest pain.

Patients who present with symptomatic new-onset AF and who manifest a history, physical signs or other evidence of significant heart failure are at higher risk for developing acute, possibly life-threatening complications. At least 1 of 4 variables present at the time of the initial evaluation—jugular venous distension, pulmonary rales, peripheral edema or a history of congestive heart failure—was detected in 13 patients (72%) in the complicated group, whereas these findings occurred in only 28 patients (35%) in the uncomplicated group. Moreover, only 2 patients (11%) in the complicated group had successful conversion to normal sinus rhythm within 6 hours in contrast to 23 of 80 patients (29%) in the uncomplicated group. Taken together, these 5 variables or "risk factors" can be ascertained within 6 hours of presentation. The presence of ≥ 1 of these 5 risk factors correctly identified all 18 patients who subsequently developed complications (sensitivity = 100%, specificity = 21%). Conversely, 17 patients (17%) of the total enrolled in the study had none of these 5 risk factors and none developed complications (negative predictive value = 100%).

Approximately 18% of patients presenting acutely with symptomatic new-onset AF are at risk for subsequent adverse events. Patients who demonstrate a history, signs or symptoms of heart failure are at highest risk for complications and should be preferentially directed to a monitored or intensive care setting. Conversely, >25% of symptomatic patients who lack clinical findings of left ventricular dysfunction may revert to normal sinus rhythm within 6 hours and appear to be at particularly low risk for cardiovascular morbidity. Because their subsequent complication risk is low, outpatient or brief inpatient management may be feasible in such cases; however, the safety and efficacy of this approach needs further study.

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Time Course of Changes in Pulmonary Vascular Resistance and the Mechanism of Regression of Pulmonary Arterial Hypertension After Balloon Mitral Valvuloplasty

Vishwa Dev, MD, DM, and Savitri Shrivastava, MD, DM

Pulmonary artery hypertension in patients with mitral stenosis is frequently out of proportion to the degree of pulmonary venous hypertension, reflecting an increase in pulmonary vascular resistance. Surgical decompression of the left atrium by closed mitral valvotomy or by mitral valve replacement has often resulted in marked regression of pulmonary hypertension.[1,2] Percutaneous balloon mitral valvuloplasty has proved to be an effective technique for the relief of obstruction in patients with mitral stenosis,[3] resulting in regression of pulmonary artery hypertension and a decrease in pulmonary vascular resistance. However, the relation of changes in pulmonary artery hypertension to the time course of changes in pulmonary venous hypertension and vascular resistance is not clear. In this report, we analyze and discuss our data to clarify this issue.

These data pertain to 53 patients (19 men, 34 women, ranging in age from 11 to 35 years) with isolated, noncalcific, severe mitral stenosis in whom balloon mitral valvuloplasty was performed in our center during the last 4 years with an anterograde transeptal approach similar to that described by Lock et al.[3] Complete hemodynamic data were obtained, including oximetries, and left ventricular angiograms were recorded before and after the procedure. A pulmonary artery follow-up angiogram was obtained after the procedure to detect any atrial shunts. In 24 patients, repeat cardiac catheterization was

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performed at 1 week; 19 of the 24 patients were restudied at 3 to 12 months after the procedure.

Immediately after balloon mitral valvuloplasty, pulmonary artery pressure decreased from 45.9 ± 13.4 to 30.1 ± 12.9 mm Hg ($p <0.001$) and pulmonary artery wedge pressure decreased from 29.0 ± 5.4 to 12.4 ± 4.1 mm Hg ($p <0.001$). Pulmonary vascular resistance did not change significantly (7.3 ± 7.1 before and 5.8 ± 5.0 U after balloon mitral valvuloplasty, difference not significant). The mean decrease in pulmonary artery pressure was similar to that in pulmonary artery wedge pressure. The mitral valve area increased from 0.71 ± 0.25 to 1.9 ± 0.8 cm^2 ($p <0.001$) and the cardiac index remained unchanged (2.9 ± 0.85 vs 3.1 ± 0.88 liters/min/m^2).

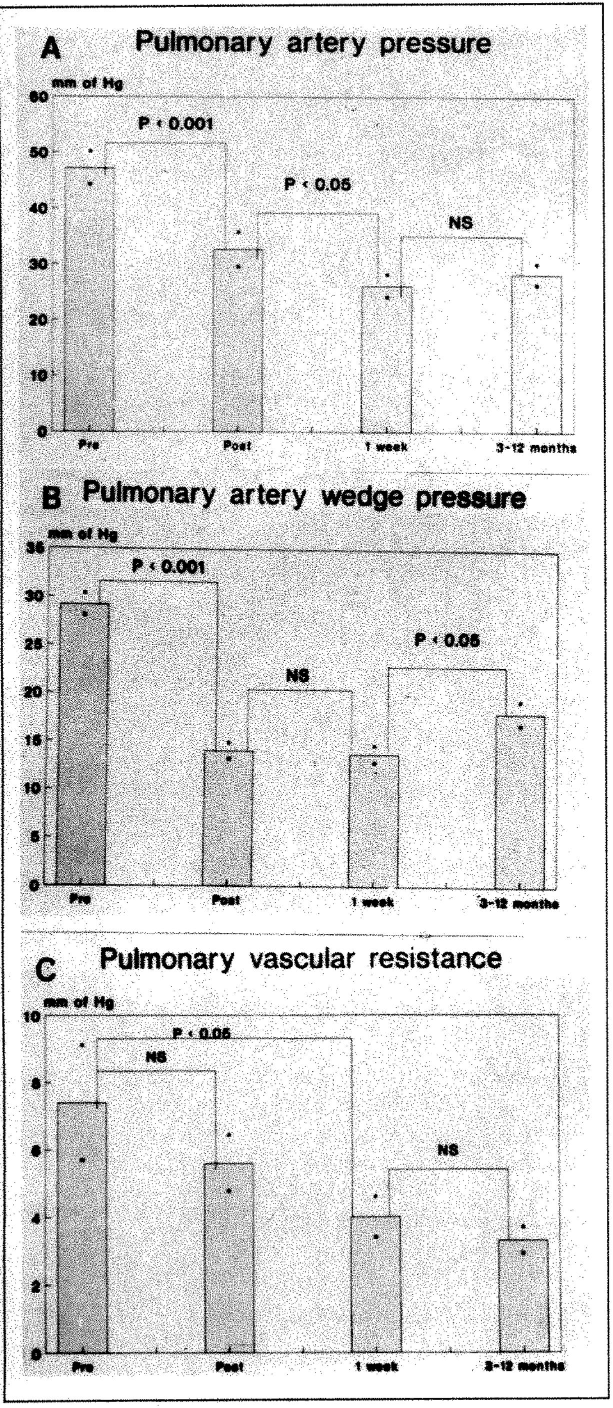

FIGURE 1. Serial changes in pulmonary artery pressure *(A)*, pulmonary artery wedge pressure *(B)*, and pulmonary vascular resistance *(C)* in 19 patients studied before (pre), immediately after (post), at 1 week and at 3 to 12 months after percutaneous balloon mitral valvoplasty. NS = difference not significant.

The time course of changes in pulmonary artery pressure, wedge pressure and vascular resistance was analyzed in 19 patients (18 treated with single-balloon and 1 with double-balloon techniques) with 4 serial sets of observations made before, immediately after, at 1 week and at 3 to 12 months after the procedure (Figure 1, Table I). Pulmonary artery pressure (Figure 1A) decreased immediately after balloon mitral valvuloplasty (from 47.5 ± 12.9 to 32.6 ± 13.5 mm Hg; $p <0.001$). At 1 week there was a further decrease in pulmonary artery pressure (to 26.1 ± 8.7 mm Hg, $p <0.05$) but no change after 1 week (28.2 ± 8.1 mm Hg at 3 to 12 months). Mean pulmonary artery wedge pressure (Figure 1B) decreased significantly immediately after balloon mitral valvuloplasty, from 29.2 ± 4.9 to 14.0 ± 3.8 mm Hg ($p <0.001$), was not changed at 1 week (13.7 ± 3.9 mm Hg; difference not significant) and increased slightly at 3 to 12 months (18.0 ± 5.4 mm Hg; $p <0.05$) because of restenosis of the mitral valve in 4 patients. Pulmonary vascular resistance (Figure 1C) changed insignificantly immediately after balloon mitral valvuloplasty (7.4 ± 5.0 to 5.6 ± 3.6 U, difference not significant). At 1 week, the decrease in pulmonary vascular resistance became statistically significant (4.0 ± 2.6 U, $p <0.05$) and did not change significantly on further follow-up (3.3 ± 1.7 U at 3 to 12 months). The decrease in mean pulmonary artery wedge pressure (from 29.2 to 14.0 ± 15.1 mm Hg) was very similar to the decrease in mean pulmonary artery pressure (from 47.5 to 32.6 ± 14.9 mm Hg). In individual data, the decrease in pulmonary artery pressure was similar to that in pulmonary wedge pressure, especially in patients whose pulmonary vascular resistance was <5 U and whose pulmonary artery diastolic pressure was similar to their pulmonary wedge pressure. The serial changes in pulmonary vascular resistance were more striking in patients with baseline pulmonary vascular resistance ≥5 units (Table I).

Two patients developed acute mitral regurgitation after the procedure. Their pulmonary vascular resistance remained unchanged immediately after valvuloplasty (11.6 and 4.2 U before and 11.4 and 4.2 U after, respectively). At 14- and 5-month follow-up, their pulmonary vascular resistance increased to 16.7 and 8.5 U, respectively. Their pulmonary artery pressure also increased after balloon mitral valvuloplasty. Four patients had persistent atrial shunt after balloon mitral valvuloplasty. Overall, the presence of atrial shunt did not appear to alter the sequential changes in pulmonary artery pressure, wedge pressure and vascular resistance after balloon mitral valvuloplasty, except that the mean decrease in pulmonary artery pressure immediately after balloon mitral valvuloplasty was less than that in pulmonary artery wedge pressure (3.8 vs 10.5 mm Hg).

Our data show that the decrease in pulmonary artery pressure immediately after balloon mitral valvuloplasty is largely passive, and is caused by the decrease in pulmonary artery wedge pressure. The degree of decrease in pulmonary artery pressure is similar to that in pulmonary artery wedge pressure, especially in patients whose pulmonary vascular resistance is <5 U and whose pulmonary artery diastolic and wedge pressures are similar. Pulmonary artery pressure decreased steadily over the next week or so and this decrease temporally coincided with the decrease in pulmonary vascular resistance. Hence, this second phase in the regression of pulmonary hypertension is due to regression of pulmonary vascular resistance. Most of the regression in pulmonary artery hypertension as well as in pulmonary vascular resistance occurs in the first week after balloon mitral valvoplasty; changes after the first week are relatively small. Occurrence of acute mitral regurgitation caused an increase in pulmonary artery pressure soon after balloon mitral valvoplasty and a gradual increase in pulmonary vascular resistance over the next 3 to 12 months. Presence of an atrial shunt did not appear to alter the changes in pulmonary vascular resistance significantly, although the mean decrease in pulmonary artery pressure was less than that in pulmonary artery wedge pressure. Increased pulmonary blood flow may account for this proportionately small decrease in pulmonary artery pressure. Levine et al[4] reported changes in pulmonary artery pressure and vascular resistance after balloon mitral valvoplasty in 14 patients with critical mitral stenosis in whom a repeat catheterization was performed at 7 ± 4 months after balloon mitral valvoplasty. They found that pulmonary artery pressure decreased immediately after the procedure (from 51 ± 17 to 40 ± 14 mm Hg) and that there was a further decrease on follow-up (to 35 ± 11 mm Hg).

TABLE I Serial Changes in Hemodynamic Data After Mitral Balloon Valvuloplasty

	Mean Pulmonary Artery Pressure (mm Hg)				Mean Pulmonary Artery Wedge Pressure (mm Hg)			
Pt. No.	Pre	Post	1 Week	3–12 Months	Pre	Post	1 Week	3–12 Months
1	55	44	30	30	27	16	17	17
2	56	38	26	24	32	10	13	16
3	52	22	16	24	28	19	14	20
4	68	48	45	35	30	18	19	18
5	38	24	18	20	30	12	10	14
6	48	28	27	20	28	14	13	12
7	32	26	22	22	24	15	13	14
8	66	66	32	38	38	22	16	23
9	36	27	27	24	32	17	17	19
10	42	25	24	22	33	14	16	14
11	50	34	28	29	32	12	16	15
12	36	22	22	22	27	11	13	14
13	26	17	15	16	22	12	8	9
14	70	30	35	30	38	6	12	20
15	58	36	35	42	32	11	11	25
16	40	17	18	42	30	10	16	30
17	50	60	28	36	28	16	16	28
18	50	28	38	38	25	15	18	18
19	30	28	10	22	18	16	3	16
Mean ± SD	47.5 ± 12.9	32.6 ± 13.5	26.1 ± 8.7	28.2 ± 8.1	29.2 ± 4.9	14.0 ± 3.8	13.7 ± 3.9	18.0 ± 5.4
	Pulmonary Vascular Resistance (U)				Mitral Valve Area (cm^2)			
Pt. No.	Pre	Post	1 Week	3–12 Months	Pre	Post	1 Week	3–12 Months
1	9.0	4.9	2.2	4.8	0.60	1.06	1.08	1.09
2	3.0	2.0	0.7	6.0	0.50	1.23	1.15	0.50
3	9.0	10.0	4.6	3.5	0.72	1.20	1.80	1.30
4	6.9	0.8	0.6	1.0	0.95	2.20	2.00	1.30
5	19.0	6.5	5.0	3.6	1.04	1.45	1.50	0.80
6	3.8	2.7	3.5	1.4	0.70	2.90	1.80	1.70
7	6.9	3.6	4.0	1.8	0.85	1.85	1.76	1.60
8	1.8	2.2	1.8	1.2	1.00	1.90	1.60	1.80
9	10.0	5.6	3.8	2.5	1.14	1.65	1.70	1.30
10	10.1	4.5	5.8	6.0	0.42	1.10	0.95	0.90
11	12.8	12.7	10.2	5.3	0.33	1.00	0.92	0.80
12	4.0	6.8	3.0	1.2	0.80	1.45	1.30	1.58
13	4.3	6.0	3.0	2.7	0.54	1.30	1.40	1.40
14	6.0	8.0	3.0	4.7	1.00	1.30	1.35	1.50
15	5.0	3.2	3.6	3.2	0.60	2.10	2.90	2.30
16	1.4	1.0	2.0	2.1	0.90	3.20	2.10	2.90
17	15.2	9.6	6.6	3.4	0.50	3.50	2.10	2.20
18	12.4	12.5	9.6	5.7	0.50	1.20	1.40	1.30
19	3.2	3.2	2.4	2.4	0.84	1.00	1.20	1.30
Mean ± SD	7.4 ± 5.0	5.6 ± 3.6	4.0 ± 2.6	3.3 ± 1.7	0.73 ± 0.24	1.72 ± 0.76	1.60 ± 0.48	1.45 ± 0.57

SD = standard deviation.

Pulmonary vascular resistance decreased insignificantly immediately after balloon mitral valvoplasty, from 630 ± 570 to 444 ± 374 dynes·s/cm^5 (difference not significant) and significantly decreased on follow-up to 280 ± 183 dynes·s/cm^5. Pulmonary artery wedge pressure decreased immediately after balloon mitral valvoplasty (from 26 ± 6 to 15 ± 5) and increased slightly on follow-up (19 ± 8 mm Hg). The mean reduction in pulmonary artery pressure immediately after balloon mitral valvoplasty (10 mm Hg) was similar to that in pulmonary artery wedge pressure (11 mm Hg). They did not study their patients at 1 or 2 weeks; thus, the time course of regression of pulmonary artery pressure could not be determined by their data.

Our data are in agreement with basic hemodynamic principles. There are 2 contributory factors to pulmonary artery hypertension in patients with mitral stenosis: (1) passive elevation of pressure due to increased pulmonary artery wedge pressure, and (2) increase in pulmonary vascular resistance. Increase in pulmonary vascular resistance possibly has 2 components: (1) spasm of the pulmonary arterioles, and (2) pulmonary vascular obstructive changes. These pulmonary vascular changes in mitral stenosis appear to be largely reversible. The passive increase in pulmonary artery pressure regresses immediately after balloon mitral valvoplasty. The increase in pulmonary artery pressure due to increased pulmonary vascular resistance regresses over the next week or so. Changes in pulmonary artery pressure and pulmonary vascular resistance after 1 week are relatively small.

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CASE REPORT

Biologic Intoxication Due to Digitalis-Like Substance After Ingestion of Cooked Toad Soup

Ming-Shyan Chern, MD, Ching-Ying Ray, BS, and Delon Wu, MD

Intoxication due to ingestion or mouthing of toads is well known to veterinarians.[1,2] Dogs and cats develop severe symptoms that often result in a lethal outcome. Salivation, cyanosis and vomiting are common manifestations in dogs after toad ingestion. Neurologic symptoms may dominate the clinical picture in severe cases. In humans, mortality and convulsive disorders have been previously observed.[3] Recently we encountered a patient with cardiopulmonary arrest and severe bradyarrhythmia after ingestion of toad soup.

A 31-year-old male labor worker was transferred to our hospital 2 hours after a successful cardiopulmonary resuscitation. He had been well until the day of admission, when he consumed a bowl of toad soup (Bufo melanosticus Schneider) that was stewed with rice wine. Thirty minutes later, he experienced nausea, vomiting, dizziness, blurred vision and general weakness, which was followed by perioral numbness and unconsciousness. He was taken to another hospital, where cardiopulmonary arrest was noted and he was successfully resuscitated. On arrival, his systolic blood pressure was 40 mm Hg, heart rate was 46 beats/min and body temperature was 36°C. The neck veins were not engorged. The lungs were clear. The heart revealed no S_3 *or* S_4 *or murmur. Liver and spleen were not palpable. There was no leg edema. An electrocardiogram revealed sinus arrest or sinus slowing with emergence of shifting atrial pacemaker and high-grade atrioventricular block; the QRS complex was normal (Figure 1A).*

The white blood cell count was 29,900/mm^3 *with a segment form of 86% and a band form of 3%; the hemoglobin was 15.0 gm/dl. Analysis of the arterial blood gas showed a pH of 7.293, a partial carbon dioxide pressure of 47.5 mm Hg, a partial oxygen pressure of 43.4 mm Hg, and a bicarbonate content of 23.0 mEq/liter. Blood chemistry values were 223 mg/dl for glucose, 1.6 mg/dl for creatinine, 129 mEq/liter for sodium, 4.2 mEq/liter for potassium, 51 U/liter for aspartate transaminase, 8.2 mg/dl for calcium and 2.0 mg/dl for phosphate. Serum creatine kinase was 215 U/liter with 100% MM fraction. A serum "digoxin" level measured on admission was 2.1 ng/ml (by fluorescence energy transfer immunoassay).*

After an intravenous bolus of 1 mg of atropine, heart rate increased to 110 beats/min and blood pressure to 100/70 mm Hg. The electrocardiogram showed a sinus rhythm at a rate of 107 beats/min and a Mobitz type I atrioventricular block (Figure 1B). A bolus of 1 mg of atropine was given every 6 hours for the subsequent 36 hours. An electrocardiogram recorded 19 hours after admission showed sinus rhythm at a rate of 58 beats/min and first-degree atrioventricular block with a PR interval of 0.22 second (Figure 1C). Three days after admission, the electrocardiogram was normal, with a sinus rate of 52 beats/min and a PR of 0.16 second (Figure 1D). The symptoms subsided gradually and the patient was asymptomatic 30 hours after ingestion of the toad soup. A repeat blood chemistry 48 hours after admission was completely normal. Follow-up serum digoxin levels were 0.7 ng/ml on day 3 and <0.4 ng/ml on day 7.

The dried extracts of the toad skin have been used as a cardiotonic agent in China (Ch'an Su) and in Japan (Senso). Some local people in Taiwan also consider toad soup a blood detoxicating agent and consume it to purify the blood. The toad venom contains many biologically active substances that are secreted primarily in the parotid gland, but are also present in skin and plasma.[1,4–6] The toxic effects of toad venom can be attributed to the glycosidic portion of the bufotoxin complex.[2] The symptoms in our patient with nausea, vomiting, dizziness, blurred vision, mental confusion, hypotension and sinus arrest with atrioventricular block are similar to symptoms of clinically severe digitalis intoxication. The high serum digoxin level measured by fluorescence energy transfer immunoassay is probably due to cross-reaction of the glycoside-like substance with the assay. There is no

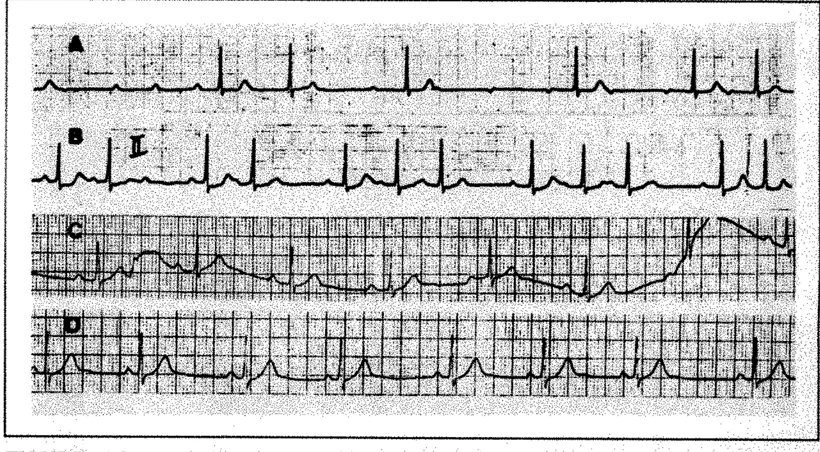

FIGURE 1. Serial electrocardiographic tracings on admission (*A*), after intravenous bolus of 1 mg of atropine (*B*), 19 hours after admission (*C*), and 3 days after admission (*D*). See text for details.

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known antidote to bufotoxin. However, propranolol has been shown to be effective in preventing ventricular fibrillation in the canine model of bufo intoxication.[2] Propranolol was contraindicated in our patient because of sinus arrest and high-grade atrioventricular block. Isoproterenol is not advised because neurologic symptoms and ventricular fibrillation may be potentiated by catecholamines. Atropine or pacemaker therapy appears to be a reasonable approach when symptoms are primarily due to bradycardia.

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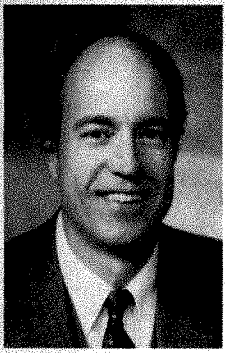
FROM THE EDITOR



"Anything To Be Done Right Has Got To Be Done By People That Make Their Living At It"

While waiting for an eye examination recently, I picked up a golf magazine and found in it a 1931 syndicated column on professional golf by the great American humorist Will Rogers. What follows are observations by Rogers on this subject, and a few comments* discussing golf and medicine.

> Well all I know is just what I read in the papers.
>
> We have had a lot of Golf Players out here in California with us lately, they are just playing a regular circuit of Tournaments. Why it's like show business in vaudeville. All the good ones are out here. By that I mean the Professionals, men who make a living at it, and a mighty good living too. They are about as fine a lot of fellows as you ever met, and fine bunch of sportsmen.
>
> You know it's a kind of funny business at that. You see these fellows don't get anything at these Tournaments unless they win it. The prizes generally run to about the first ten. Well sometimes there is sixty or eighty that start, so you can see somebody has got to have some other visible means of support than his "Putter." They pay their railroad fare and all their living expenses and if they can't find that Gopher Hole in less knocks than the other sixty why, it's just too bad.
>
> I saw 'em all playing in the $10,000 Professional Championship, where the winner got I think $3500. Now Golf is no joke when it gets into jack like that, I have done my fair share of kidding about it, but when there is $3500 bucks strung along on the green and you have to project a little Gutapercha missle into the empty end of a sardine can twenty feet away to get your clutches onto any part of that dough, I want to tell you neighbors the humor of the game immediately vanishes into cold prespiration....
>
> You are shooting for your marmalade on every shot, on every hole, on every day, the thing lasts. There is no three strikes here.... Every move is the big one. When one is sliced out into the forest reserve nothing goes with it but your week's board bill, and fare to the next Niblick Rodeo. There is not only a story, but a meal hanging on every putt. You just get the worry of one hole out of your system and onto your handkerchief, then all you have to do is walk up to a nearby executioneer's stand, and look from there down across a beautiful valley... and by exact geometrical survey just 543 yards and ⅞th inches is located another of these cunning little resepticles in the ground with a mouth no bigger than a Higlander's heart, and to give aid and comfort to you in distress there is a well painted sign staring you in the face with the information that if you are any kind of a Golfer whatever that four swipes at this little cascaret is all that "Should" be required. That any you take over that, you are simply deducting from your own Bank account.
>
> Then there is a pardner, or accomplice, who plays along with you. You are not sent out for company but to annoy each other, if it wasent for watching what he was doing you could do pretty good. Sometimes it's (what I think) is called a match play that is all you have to beat is the Guy with you. But generally it's medal play, (I think that's it) then all you have to beat is eighty professionals (that you know in your own heart are better than you) and Bobby Jones, and Par, and O.B. Keelers Typewriter....

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*I was not particularly pleased with the "comments" I initially developed and asked my brother, Dr. Stewart R. Roberts, Jr. (Emory Clinic), for help. The resulting "comments" therefore are those of both of us.

> Then there is wives. Yes Sir these fellows actually have wives, and they are following around. What must those poor creatures go through. They all look young. I guess there never was an old woman Golfer's wife, either the strain or starvation get 'em along before middle life. I would think one tough season of tournament would wear out about three wives on a fellow. Think of the prospects of a new dress hanging on every approach. If he goes in the bunker she goes back to last years "Cerise." Just think of having to see your husband's every mistake. Other wives know of them, but they don't see 'em happen. Not only you seeing what a fool he has made of himself by missing a ten inch putt, "But it was right before everybody. What must they think?" Then when you get through the game, the strain is not over, you have to wait till the last Guy comes in at sundown to find out what happened to you. Oh, It's a game, don't kid yourself about that. I don't mean this Junk these old fat Birds go out and call Golf, I mean it's a game when you have to do it right, or you don't eat. Anything to be done right has got to be done by people that make their living at it, like football, look what it has done since it's for the old ham and eggs.
>
> But these Golfers are a cheerful lot, win or lose, wives and all. They laugh it off, take the husband home, dress him up and send him back for another beating on the morrow. But don't kid yourself Comrades that there is nothing to this game. Put $3500 smackers down and tell us we had one putt to win it. I think I would be so nervous I would pick up the caddy and swing him at it.

It is true for both the golfer and the physician that the best work is done by those who earn their living at it. The best scores are not shot by the weekend golfer or the part-time physician. The full-time physician is more available and usually more experienced than the part-time physician. The physician-clinical researcher is being replaced by the full-time physician and the full-time researcher, now often a PhD rather than an MD. Whether practice, research, or administration, "doctoring" increasingly requires the single-minded purpose and quality of work provided by those who "make their living at it."

Back in Will Rogers' day, the gutta-percha golf ball was in play. That golf ball has undergone about as much change as has medicine in the past 60 years. But although the course and tools (clubs) of both golf and medicine continue to change, the stance and swing of both the golfer and the physician remain the same. Compared to yesterday the golf courses today are tougher, but the professional golfers of today are better. Medicine today is much more complex and difficult, of course, than yesterday. Third-party intervention and waiting lawyers are like being in the rough most of the time. The patients in hospitals in the USA today are required to be sicker than those of yesterday, their length of stay is shorter, and their discharge sooner. Hospitalization for a diagnostic workup is a thing of the past. Today's golf course of medicine is longer, contains more sandtraps, more "dog-legs," and less flat greens than the one of yesterday, but physicians—as have the professional golfers—have risen to the challenge. The present day ones are better and provide better care than those of the past.

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

Portions of "Golf is Good—When There's Dough in It!" are reprinted courtesy of the Will Rogers Memorial, Claremore, Oklahoma.

re prescribing, please see full prescribing information.
ief Summary follows.

NTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary
ary cirrhosis.
2. Preexisting gallbladder disease (See WARNINGS).
3. Hypersensitivity to gemfibrozil.

ARNINGS. 1. Because of chemical, pharmacological, and clinical similarities be-
ween gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical
udies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug
ject, 1000 subjects with previous myocardial infarction were treated for five years
clofibrate. There was no difference in mortality between the clofibrate-treated sub-
s and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects
eloped cholelithiasis and cholecystitis requiring surgery. In the other study, con-
cted by the World Health Organization (WHO), 5000 subjects without known cor-
ary heart disease were treated with clofibrate for five years and followed one year
ond. There was a statistically significant, 29%, higher total mortality in the clofibrate-
ated than in a comparable placebo-treated control group. The excess mortality was
to a 33% increase in noncardiovascular causes, including malignancy, post-
lecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated
jects for gallbladder disease was confirmed.
uring the Helsinki Heart Study and in the 1½ year follow-up period since the trial
completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55
%) in the placebo group. Mortality from any cause during the double-blind portion
e study was 44 deaths in the Lopid group and 43 in the placebo group. Because of
ore limited size of the Helsinki Heart Study, this result is not statistically-
icantly different from the 29% excess mortality seen in the clofibrate group in the
rate WHO study. Noncoronary heart disease related mortality showed a 58%
er trend in the Lopid group (43 vs 27 patients in the placebo group, $p=0.056$).
he Helsinki Heart Study, the incidence of total malignancies discovered during the
nd in the 1½ years since the trial was completed was 39 in the Lopid group and 29
placebo group (difference not statistically significant). This includes 5 basal cell
nomas in the Lopid group and none in the placebo group ($p=0.06$; historical data
dicted an expected 4.7 cases in the placebo group). GI malignancies and deaths
m malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

LOPID®

BID

(gemfibrozil) 600-mg Tablets

RAISES HDL...DRAMATICALLY
REDUCES HEART ATTACK

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p=0.1$). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%). **Gallbladder surgery** was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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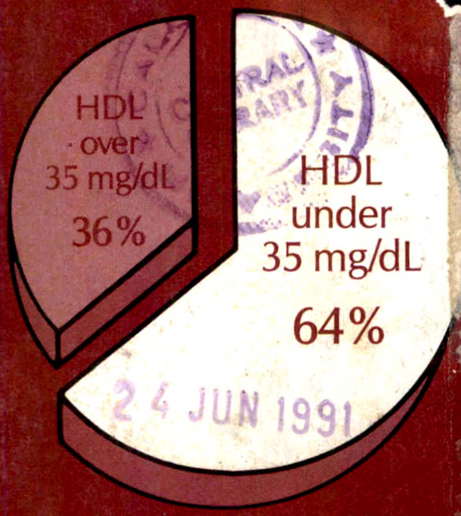
What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol *and* triglycerides—are common among heart attack victims,[1] and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.[2]


HEART ATTACK PATIENTS (PROCAM TRIAL)[2]

24 JUN 1991

LOPID raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).[3]

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).[3]

A powerful case for

LOPID® BID

(*gemfibrozil*) 600-mg Tablets

RAISES HDL...DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

References: 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest*. 1973;52:1533-1543. **2.** Assmann G, Schulte H. *PROCAM-Trial: Prospective Cardiovascular Münster Trial*. Zürich: Panscientia Verlag; 1986:8-9. **3.** Data on file, Medical Affairs Dept, Parke-Davis.

Please see adjacent page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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